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Tendon Injuries

Basic Science and Clinical Medicine

Springer

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Preface

Standard textbooks of anatomy, physiology, pathology, orthopedic surgery, and sports medicine provide little information on tendons. Tendon ailments are increasingly prevalent in orthopedic surgery and sports medicine, and in occupational and family medicine as well.

This book provides a comprehensive presentation on human tendons for a wide range of readers, from students and teachers of physical education, biomechanics, medicine, and physical therapy to specialists such as orthopaedic surgeons, pathologists, and physicians specializing in sports medicine. We describe the current principles of diagnosis, treatment, and rehabilitation of tendon injuries and disorders. Although we acknowledge that these principles are constantly changing, this book gives readers the tools presently available to the scientific and biomedical community to tackle tendon problems. This book has been conceived to be used as a comprehensive source for physicians, surgeons, physical therapists, chiropractors, sports coaches, athletes, fitness enthusiasts, and students in a variety of disciplines.

The book is definitely a medical book, but with appeal to professionals outside the medical field.

The editors have collectively more than 70 years of experience in orthopaedic sports medicine, and have dedicated much of their research efforts to studying the pathophysiology of tendon problems. We believe that, as a team, our knowledge and experience will give help and guidance in the management of tendon problems.

In recent years—at least in the West—the demand for heavy physical work has markedly decreased. Conversely, leisure-time sports activities have become more popular, frequent, and intense. Repetitive work, excessive weight, poor fitness, and the lack of regular exercise and of variation in physical loading have all contributed to the increased incidence of degenerative changes in the musculoskeletal system. Tendon problems are seen frequently in nonathletes. Modern athletes also suffer from tendon ailments. The biological limits that musculoskeletal tissues can withstand are exceeded, with overuse and acute injuries, especially in tendons.

This book provides principles of diagnosis, treatment, and rehabilitation for various tendon problems. We envisage the book to be heavily used by physicians, surgeons, physical therapists, athletic trainers, and other professionals treating patients with tendon problems.

We would not have been able to write this book without the help of our coauthors from all over the world. To them, our thanks and appreciation.

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Part I
Basic Sciences, Etiology, Pathomechanics, and Imaging

1
Anatomy of Tendons

Moira O'Brien

A **tendon** forms an integral part of a musculotendinous unit. Its primary function is to transmit forces from muscle to rigid bone levers producing joint motion [1,2]. Tendons are stronger than muscles, are subjected to both tensile and high compressive forces, and can sustain 17 times body weight. They act as shock absorbers, energy storage sites, and help to maintain posture through their proprioceptive properties [3]. High rates of loading make tendons more brittle, thus absorbing less energy, but being more effective moving heavy loads [4]. The converse occurs at low rates of loading, when tendons are more viscous, absorb more energy, and are less effective at moving loads [4].

Tendons generally tend to concentrate the pull of a muscle on a small area. This enables the muscle to change the direction of pull and to act from a distance. A tendon also enables the muscle belly to be at an optimal distance from a joint without requiring an extended length of muscle between the origin and insertion.

The range of motion of a musculotendinous unit and the force applied to the tendon determine the orientation of the fibers, relative to the axis of the tendon. The greater the longitudinal array of the muscle fibers, the greater the range of motion of the muscle and the tendon. The strength of a tendon depends on the number, size and orientation of the collagen fibers. It also depends on the thickness and internal fibrillar organization [5] (see Figures 1-1 and 1-2).

Collagen fibers are distributed in different patterns. In tendons, where tension is exerted in all directions, the fiber bundles are interwoven without regular orientation, and the tissues are irregularly arranged. If tension is in only one direction, the fibers have an orderly parallel arrangement, i.e. are regularly arranged. In most regions, collagenous fibers are the main component.

Fusiform muscles exert greater tensile force on their tendons than pennate muscles because all the force is applied in series with the longitudinal axis of the tendon. The more oblique the muscle fibers, the more force is dissipated laterally, relative to the axis of the tendon. The occupation and sports activity of the individual may alter the alignment of the fibers of the tendon.

The majority of the fibers run in the direction of stress [6] with a spiral component, and some fibers run perpendicular to the line of stress [7]. Small-diameter fibers may run the full length of a long tendon [8], but fibers with a diameter greater than 1500 Å may not extend the full length of a long tendon [9].

The details of the gross anatomy of some tendons have been known for some time, but the finer details and variations of a large number of tendons have not often been emphasized. For example, the spiral arrangement of the fibers of the tendon of flexor digitorum superficialis as they flatten, fork, and fold around the flexor digitorum profundus to allow it to reach its insertion into the distal phalanx of the hand and the similar arrangement of the flexor digitorum brevis and the longus in the foot have only recently been clarified (see Figure 1-3).

Tendons were usually described as having a parallel orientation of collagen fibers [10] until transmission and scanning electron microscopy demonstrated that collagen fibrils are orientated longitudinally, transversely, and horizontally. The longitudinal fibrils cross each other, forming spirals and plaits [11,12]. Transmission and scanning electron microscopy have demonstrated that the interior of the tendon consists mainly of longitudinal fibrils with some transverse and horizontal collagen fibrils [11].

Tendons vary in shape and size. They may be flattened or rounded. They may be found at the origin or insertion of a muscle, or form tendinous intersections within a muscle. An aponeurosis is a flattened tendon, consisting of several layers of densely arranged collagen fibers. The fascicles are parallel in one layer but run in different directions in adjacent layers. The aponeurosis may form a major portion of a muscle, e.g. the external oblique, internal oblique, and transversus abdominis muscles. The aponeurosis of the external oblique forms part of the

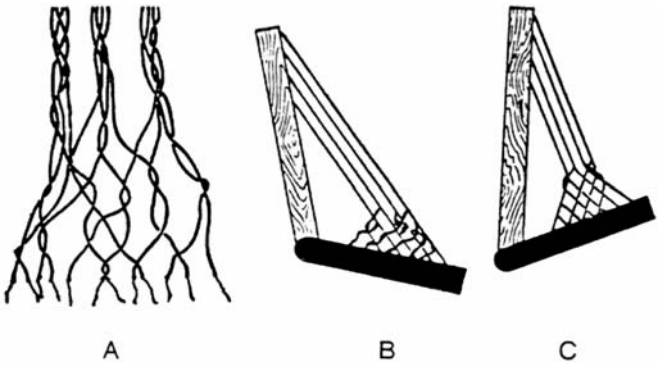

FIGURE 1-1. (A) Diagram of the inferior attachment of a tendon showing plaited component fibers. (B and C) Different fibers take the strain in different positions of a joint.

rectus sheath, the inguinal ligament, and lacunar ligaments. The aponeurosis of the internal oblique and transversus form the conjoint tendon, which takes part in the formation of the lower portion of the anterior wall of the rectus sheath and the medial part of the posterior wall of the inguinal canal. The bicipital aponeurosis of the biceps brachii extends its insertion into the ulna. Laminated tendons are found in the pectoralis major, latissimus dorsi, and masseter muscles.

Tendons may give rise to fleshy muscles, e.g. the lumbricals, arising from the flexor digitorum profundus tendons in the hand and the flexor digitorum longus in the foot. The oblique fibers of the vastus medialis arise from the tendon of the adductor magnus. The oblique fibers of the vastus lateralis arise from the iliotibial tract. The semimembranosus tendon has several expansions that form ligaments including the oblique popliteal ligament of the knee and the fascia covering the popliteus muscle (Figure 1-4).

Segmental muscles that develop from myotomes often have tendinous intersections. In certain areas each segment has its own blood and nerve supply. These include the rectus abdominis, the hamstrings, and the sternocleidomastoid.

Sesamoid bones may develop in tendons where they cross articular surfaces or bone: They are present as

FIGURE 1-2. Multipennate.

cartilaginous nodules in the fetus. In the upper limb, sesamoid bones are found on the palmar aspect in the upper limb, in the insertion of the two heads of the adductor pollicis on the ulnar side, and in the flexor pollicis brevis at its insertion into the radial side of the base of the proximal phalanx of the thumb. The pisiform is a sesamoid in the tendon of the flexor carpi ulnaris. A sesamoid is occasionally found in the biceps brachii tendon in relation to the radial tuberosity.

The patella in the tendon of the quadriceps is the largest sesamoid in the body (see Figure 1-5). There is occasionally a sesamoid in the lateral head of the gastrocnemius (fabella), in the tibialis anterior, opposite the distal aspect of the medial cuneiform, or in the tibialis posterior below the plantar calcaneonavicular ligament,

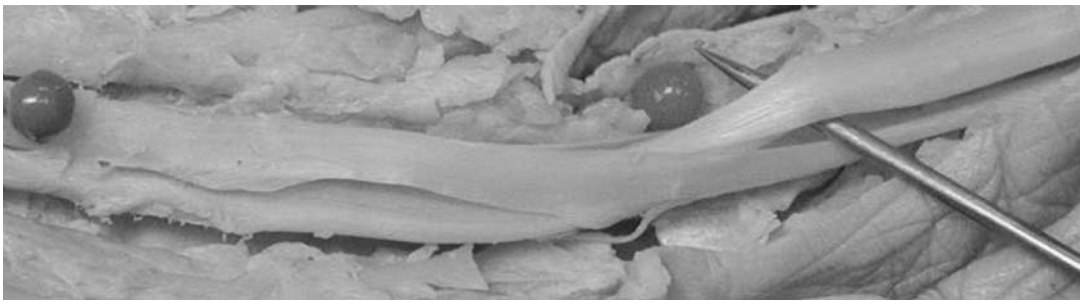

FIGURE 1-3. Flexor digitorum superficialis flattens, forks, and folds to allow flexor digitorum profundus to insert into distal phalanx.

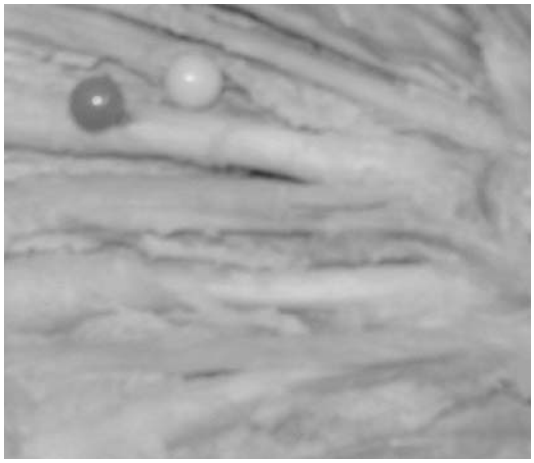

FIGURE 1-4. Lumbricals arising from tendons of flexor digitorum profundus in the hand.

the spring ligament [13]. A sesamoid may occur in the peroneus longus tendon before it enters the groove in the cuboid. There are always two sesamoid bones associated with the insertion of the flexor hallucis brevis. The medial, the larger, is found in the abductor hallucis and the medial half of the flexor hallucis brevis. The lateral is in the combined insertion of the lateral half of the flexor hallucis brevis and the adductor hallucis. The medial sesamoid may be bipartite, usually a bilateral feature [14] (see Figure 1-5).

Tendons may be intracapsular, e.g. the long head of the biceps brachii and the popliteus. The synovial membrane of the joint surrounds the tendons inside the joint and extends for a variable distance beyond the joint itself [15]. The knowledge of the extent of the synovial covering is important when deciding to inject around a joint. The synovial sheath, which surrounds the long head of the biceps brachii, extends to the lower border of the latissimus dorsi insertion, approximately the lower border of the posterior fold of the axilla.

Tendons are covered by fibrous sheaths, or retinacula, as they pass over bony prominences or lie in grooves lined with fibrocartilage to prevent them from bowstringing when the muscle contracts [15]. Reflection pulleys hold tendons as they pass over a curved area, e.g. the transverse humeral ligament that holds the long head of the biceps as it leaves the shoulder joint and the superior and inferior peroneal retinacula surrounding the peroneus longus and peroneus brevis. Fibrocartilage was present in 22 of 38 tendon sites where tendons pressed against bone [3]. Most retinacula are mainly fibrous, but the inferior peroneal retinaculum and the trochlear retinaculum in the orbit for the superior oblique muscle are cartilaginous [3] (see Figure 1-6).

When tendons run in fibro-osseous tunnels or pass under retinacula, fascial slings bind them down; they are enclosed in synovial membrane. The membrane consists of two continuous, concentric layers, which are separated by a film of fluid. The visceral layer surrounds the tendon, and the parietal is attached to the adjacent connective tissues. As a tendon invaginates into the sheath, there is often a mesotendon.

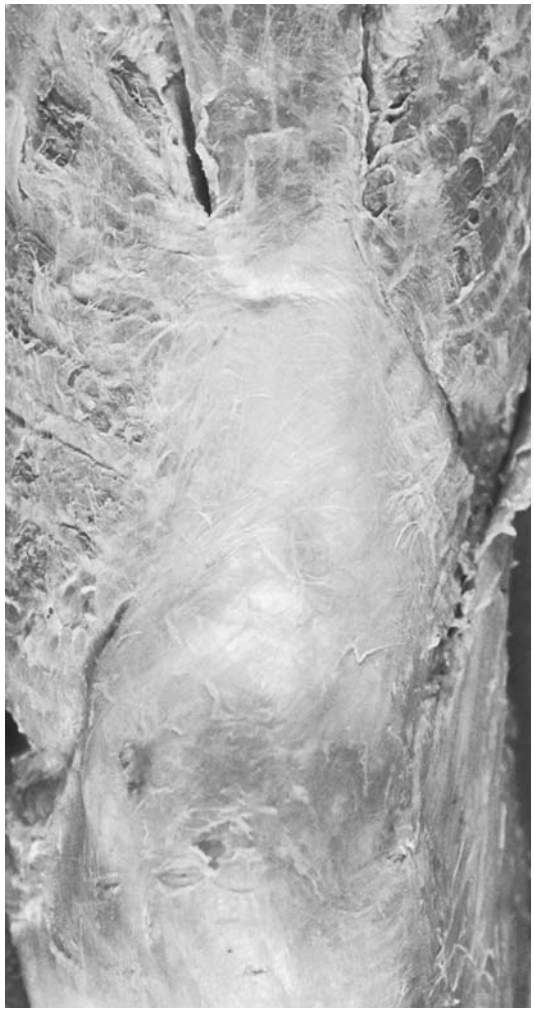

FIGURE 1-5. Patella in quadriceps tendon.

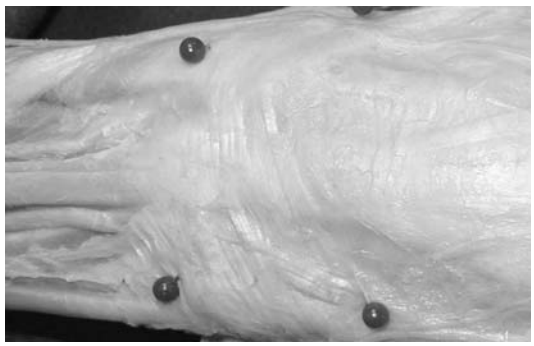

FIGURE 1-6. Extensor retinaculum of wrist.

Synovial folds in the fibro-osseous sheaths of the phalanges of the hand and foot are called the vincula longa and vincula brevia. They contain the blood vessels that supply the flexor tendons inside the sheaths. The longa are thinner, and are found proximally; the brevia are shorter, and are found at the insertions of the tendons. The lining of the sheath is extremely cellular and vascular. It secretes synovial fluid, and reacts to inflammation by cellular proliferation and the formation of more fluid. This may result in adhesions and restriction of movement between the two layers.

Bursae are associated with many tendons and help to reduce friction between 1) tendons, e.g. the tibial intertendinous bursae at the insertions of the tendons of sartorius, gracilis, and semitendinosus; 2) tendons and aponeurosis, e.g. the gluteus maximus and aponeurosis of vastus lateralis; 3) tendons and bone; 4) deep infrapatellar bursae, e.g. the ligamentum patellae and tibial tuberosity, subacromial bursa, and retrocalcaneal bursa. The olecranon bursa and the superficial infrapatellar bursa are examples of bursae between tendons and skin.

Arthroscopy, magnetic resonance imaging (MRI), and ultrasound have emphasized the prevalence of variations in muscles and tendons. The variations in the anatomy may affect the entry of an arthroscope or cause difficulty in interpretation of MRI studies. The attachments of the long head of the biceps to the supraglenoid tubercle and the superior margin of the glenoid labrum are intracapsular, and may be involved in a Type IV superior labrum anterior-posterior (SLAP) lesion, when there is a bucket-handle tear of the superior labrum with extension of the tear into the biceps tendon [16].

Supernumerary tendons may occur. The most common tendon in the lower limb to have an accessory tendon is the soleus muscle-tendon complex. When present, it may have its own tendon of insertion anterior to the soleus [9]. The plantaris may also be duplicated. Supernumerary tendons have been reported in the tibialis anterior, tibialis posterior and peroneus longus [9]. The plantaris in the leg and the palmaris longus in the forearm are the most frequent tendons that may be absent.

Musculotendinous Junction

Tendons develop independently in the mesenchyme, and their connection with their muscle is secondary. The myotendinous junction is the junctional area between the muscle and the tendon and is subjected to great mechanical stress during the transmission of muscular contractile force to the tendon [2]. The extension of a tendon's collagen fibers into the body of the muscle increases the anchoring surface area [9]. It can continue as a single or as multiple visible structures or as a diffuse network, visible only under a microscope. The arrangement of the tendinous fibers is tailored to direct the force generated by the muscular contraction to the point of insertion.

The **musculotendinous junction** is considered the growth plate of muscle, as it contains cells that can elongate rapidly and deposit collagen. The tendon elongates here. It is a complex area that contains the organs of Golgi and nerve receptors. The muscle fibers may show terminal expansions. Electron microscopy shows that these ends have a highly indented sarcolemma, with a dense internal layer of cytoplasm into which the actin filaments of the adjacent sarcomeres are inserted [17]. The basement membrane is prominent, and the collagen and reticulum fibers lie in close contact. Subsarcolemmal deposits of dystrophin occur at the junctional folds and the extrajunctional sarcolemma of the myotendinous junction, suggesting that dystrophin may be one of the compounds linking terminal actin filaments to the subplasmalemmal surface of the junctional folds of the myotendon [9].

Muscle tears tend to occur at the musculotendinous attachments [18]. Variations in the extent of the tendon into the muscle at the origin and insertion may explain the site of muscle tears. There are variations in the shape and extent of the adductor longus tendon. Tendinous intersections are found in the hamstrings denoting the original myotomes [19] (see Figure 1-7).

FIGURE 1-7. Musculotendinous junction of adductor longus.

Osteotendinous Junction

The insertion of a tendon into bone, or the osteotendinous junction (OTJ), involves a gradual transition from tendon to fibrocartilage to lamellar bone, and consists of 4 zones of pure fibrous tissue, unmineralized fibrocartilage, mineralized fibrocartilage, and bone [20]. There are one or more prominent basophilic lines (cement or blue lines), called the tidemark. The tidemark represents the outer limit of the mineralized fibrocartilage. The line is usually smoother than at the osteochondral junction. Chondrocytes are found on the tendon side of the tidemark, and tendon fibers can extend as far as the osteochondral junction. Very few blood vessels cross from bone to tendon. Collagen fibers often meet the tidemark at right angles, i.e. there is a change in the angle just before the tendon becomes cartilaginous, and only a gradual change occurs inside the fibrocartilage. If the attachment is very close to the articular cartilage, the zone of fibrocartilage is continuous with the articular cartilage. Under electron microscopy, it is found to be composed of densely packed, randomly oriented collagen fibrils of varying diameters that are continuous with those of the unmineralized and mineralized fibrocartilage. The chemical composition of fibrocartilage is age dependent, both in the OTJ and other fibrocartilaginous zones of the tendon.

Osteogenesis at a tendon-bone junction allows a smooth mechanical transition. Periosteum is specialized, dense connective tissue, and has an outer vascularized layer that is mostly fibrous, and an inner cellular layer. It possesses osteogenic potential, except where tendons are inserted. The periosteum is connected to the underlying bone by dense collagen fibers, extending its outer fibrous layer into the mineralized bone matrix perpendicular to the bone surface. During bone growth, collagen fibers from the tendon are anchored deeper into the deposited bone. Variations in the attachments of tendon to bone may explain the variations in hot spots on bone scans when stress fractures are present in the tibia [21].

A tendon can be attached to bone in several ways. The insertion may be to the epiphysis or to the diaphysis. It may be a fleshy attachment to the periosteum or a tendinous attachment to a bony crest, ridge, or prominence. Fleshy attachments produce smooth, featureless surfaces indistinguishable from areas of bone covered by periosteum alone, but attachments of tendons, aponeurosis, and fibrous septa produce distinct markings e.g. tubercles or ridges [20].

There is no periosteum if fibrocartilage is present at the tendon attachment [20]. Benjamin et al. [20] found that most tendons attached to the ends of long bones had fibrocartilage at their attachments, but the amount of fibrocartilage varied. Fibrocartilage was usually most obvious in the portion of the tendon nearest a joint, e.g. the supraspinatus. The fibrocartilage acts as a stretching brake, as a stretched tendon tends to narrow, but the cartilage matrix prevents this so that it does not stretch at its interface with bone. The structure of the attachment zone of a tendon may vary, depending on the occupation and sports activity of the individual [22]. The insertion of the biceps of a window cleaner, who works with his forearm pronated, would differ from that of an individual who works with the forearm supinated.

Nerve Supply

Tendons are supplied by sensory nerves from the overlying superficial nerves or from nearby deep nerves. The nerve supply is largely, if not exclusively, afferent. The afferent receptors are found near the musculotendinous junction [23], either on the surface or in the tendon. The nerves tend to form a longitudinal plexus and enter via the septa of the endotenon or the mesotendon if there is a synovial sheath. Branches also pass from the paratenon via the epitenon to reach the surface or the interior of a tendon [16].

There are 4 types of receptors. Type I receptors, called Ruffini corpuscles, are pressure receptors that are very sensitive to stretch and adapt slowly [24]. Ruffini corpuscles are oval and 200 µm by 400 µm in diameter. Type II receptors, the Vater-Pacini corpuscles, are activated by any movement. Type III receptors, the Golgi tendon organs, are mechanoreceptors. They consist of unmyelinated nerve endings encapsulated by endoneural tissue. They lie in series with the extrafusal fibers and monitor increases in muscle tension rather than length. The Golgi tendon organ is 100 µm in diameter and 500 µm in length. The tendon fiber is less compact here than in the rest of the tendon. The endoneural tissue encapsulates the unmyelinated nerve fibers. The lamellated corpuscles respond to stimuli transmitted by the surrounding tissues, e.g. pressure, which is produced by muscle contraction. The amount of pressure depends on the force of contraction. They may provide a more finely tuned feedback. Type IV receptors are the free nerve endings that act as pain receptors.

Blood Supply

The blood supply of tendons is very variable, and is usually divided into three regions: 1) The musculotendinous junction; 2) the length of the tendon; and 3) the tendon-bone junction. The blood vessels originate from vessels in the perimysium, periosteum, and via the paratenon and mesotendon.

The blood supply to the musculotendinous junction is from the superficial vessels in the surrounding tissues.

Small arteries branch and supply both muscles and tendons, but they are completely separate as there is no anastomosis between the capillaries.

The main blood supply to the middle portion of the tendon is via the paratenon. In tendons that are exposed to friction and are enclosed in a synovial sheath, it is via the vincula (see Figure 1-8). The small blood vessels in the paratenon run transversely towards the tendon, and branch several times before running parallel to the long axis of the tendon. The vessels enter the tendon along the endotenon; the arterioles run longitudinally flanked by two venules. Capillaries loop from the arterioles to the venules, but they do not penetrate the collagen bundles (see Figure 1-9).

Vessels supplying the bone-tendon junction supply the lower one-third of the tendon. There is no direct communication between the vessels because of the fibrocartilaginous layer between the tendon and bone, but there is some indirect anastomosis between the vessels. Tendons that go around corners are subject to greater strain, and are more likely to have interference with their blood supply, particularly if they cross an articular surface, as they may also be subjected to compressive forces, which may result in cartilaginous changes in the tendon from Type I to Type II collagen.

The blood supply of tendons is compromised at sites of friction, torsion, or compression. This is found particularly in the tibialis posterior, supraspinatus, and Achilles tendons [25–27]. There is a characteristic vascular pattern in the rotator cuff tendons, with a constant area of reactive avascularity approximately 0.7 to 1 cm from the insertion. This critical area is the junction between the two groups of blood vessels, supplying the muscular and tendinous portions and between the anterior and posterior vessels. There is now evidence that there is an area of hypervascularity secondary to low-grade inflammation with neovascularization due to mechanical irritation in the critical zone of the supraspinatus [26].

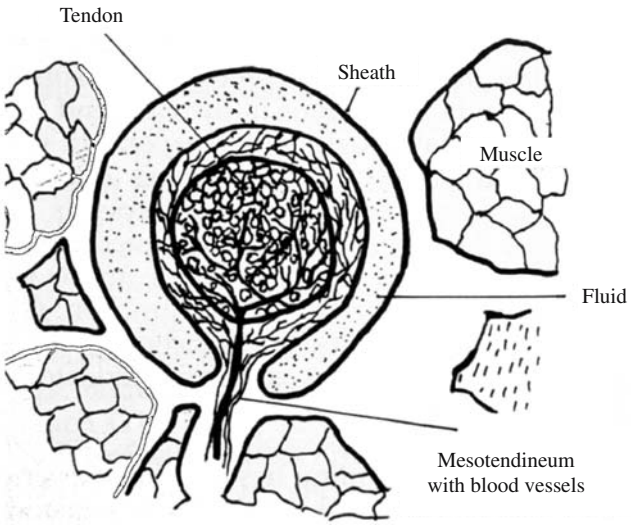

Figure 1-8. Blood supply of tendon surrounded by a synovial sheath.

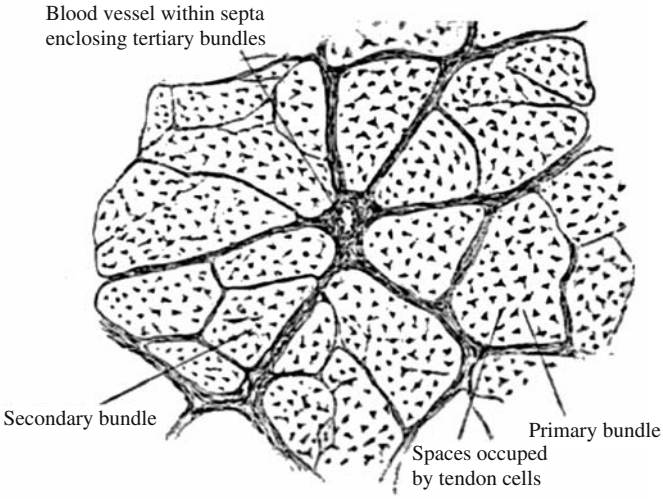

Figure 1-9. Transverse section of tendon.

The blood supply of the flexor tendons of the hand can be divided into two regions. The blood supply of the synovial-covered tendons consists of longitudinal vascular bundles with short transverse anastomosis, while non-synovial-covered tendons with paratenon have a uniform blood supply. The synovial-covered portions of the flexor digitorum superficialis and the flexor digitorum profundus receive their blood supply only on the dorsal aspect. There are avascular regions at the metacarpophalangeal joint and at the proximal interphalangeal joint, possibly resulting from the mechanical forces exerted at these zones [27]. The long flexor tendons are supplied by two main sources: primarily by small arteries that run in the vincula longa and brevia and reach the dorsal surface of the tendon; and secondarily by small intrinsic longitudinal vessels that run parallel to the collagen fibers of the tendon and extend from the muscular attachments of the long flexor tendons.

The **Achilles tendon** is supplied at its musculotendinous junction, along the length of the tendon, and at its junction with bone. The blood supply consists mainly of longitudinal arteries that course the length of the tendon. The area of lowest vascularity is 2 to 6 cm above the insertion of the tendon. The Achilles tendon is the thickest and the strongest tendon. It is approximately 15 cm long, and on its anterior surface it receives the muscular fibers from the soleus almost to its insertion. The tendon is at first flattened at its junction with the gastrocnemius, and then it becomes rounded. It expands at its insertion, where it becomes cartilaginous [9]. The soleus and the gastrocne-

mius vary in their contribution to the Achilles tendon and in the extent of their fusion. The soleus varies from 3 to 11 cm, and the gastrocnemius from 11 to 16 cm. As the tendon descends it twists, and the gastrocnemius is found mainly on the lateral and posterior part of the tendon. Rotation begins above the region where the soleus tends to join, and the degree of rotation is greater if there is minimal fusion [9]. The twisting produces an area of stress in the tendon, which is most marked 2 to 5 cm above the insertion, which is the area of poor vascularity and a common site of tendon ailments [28–30].

Structure of Tendons

Tendons appear white, as they are relatively avascular. A tendon is a roughly uniaxial composite, composed mainly of Type I collagen in an extracellular matrix composed mainly of mucopolysaccharides and a proteoglycan gel [31]. Tendons consist of 30% collagen and 2% elastin embedded in an extracellular matrix containing 68% water and tenocytes [33]. Elastin contributes to the flexibility of the tendon. The collagen protein tropocollagen forms 65% to 80% of the mass of dry weight tendons and ligament (see Figure 1-10).

Ligaments and tendons differ from other connective tissues in that they consist mainly of Type I collagen. Ligaments have 9% to 12% of Type III collagen, and are more cellular than tendons [34]. Type II collagen is found abundantly in the fibrocartilage at the attachment zone of the tendon (OTJ) and is also present in tendons that wrap around bony pulleys. Collagen consists of clearly defined, parallel, and wavy bundles. Collagen has a characteristic reflective appearance under polarized light. Between the collagen bundles, fairly evenly spaced there are sparse cells. Cross-section of tendons shows inactive fibroblast cells [35].

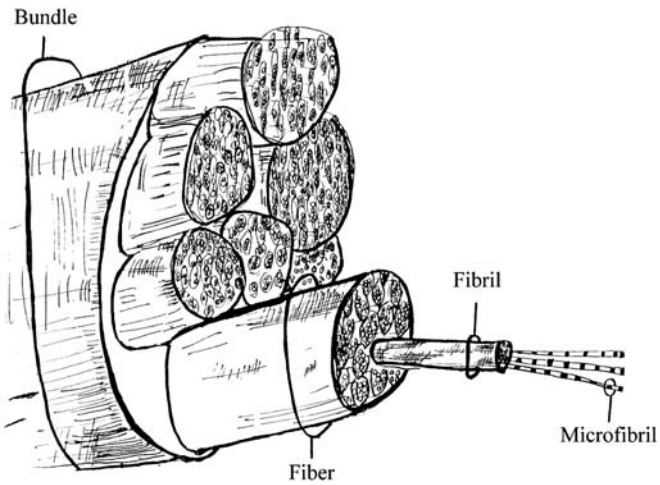

FIGURE 1-10. Schematic drawing of a tendon.

Five tropocollagen units unite to form fibrils. Several parallel fibrils embedded in the extracellular matrix constitute a fiber. A group of fibers constitute a fascicle, the smallest collagenous structure that can be tested [36]. Fascicles are surrounded by endotenon, epitenon, and paratenon. The endotenon is a mesh of loose connective tissue, which surrounds collagen bundles. The endotenon holds the bundles together, permits some movement of the bundles relative to each other, and carries blood vessels, lymphatics, and nerves. A fine connective tissue sheath, the epitenon, is continuous throughout the inner surface with the endotenon, and surrounds the whole tendon [35]. The paratenon is the outermost layer and is composed of loose, fatty, areolar tissue surrounding the tendon: Nerves and blood vessels run through it. Fluid may be found between the paratenon and the epitenon, preventing friction [31]. Its mechanical function is to allow the tendon to glide freely against the surrounding tissue. The connective tissue that surrounds the fibrils, the fascicles, and the entire muscle consists mainly of Type I collagen, with a minor component consisting of Type III collagen. Type IV collagen is found in the basement membrane, with traces of Type V collagen.

Collagen Formation

The structural unit of collagen is tropocollagen, a long, thin protein 280 nm long and 1.5 nm wide, which consists mainly of Type I collagen [33] (see Figure 1-11). Tropocollagen is formed in the fibroblast cell as procollagen, which is then secreted and cleaved extracellularly to become collagen. The 100 amino acids join to form an alpha-chain. There are 3 alpha-chains, which are surrounded by a thin layer of proteoglycans and glycosaminoglycans. Two of the alpha-chains are identical (alpha-1), and one differs slightly (alpha-2). The three-polypeptide chains each form a left-handed helix. The chains are connected by hydrogen bonds and wind together to form a ropelike, right-handed superhelix [37], which gives the collagen molecule a rodlike shape [37]. Almost two-thirds of the collagen molecule consists of 3 amino acids: glycine (33%), proline (15%), and hydroxyproline (15%). Each alpha-chain consists of a repeating triplet of glycine and two other amino acids. Glycine is found at every third residue, while proline (15%) and hydroxyproline (15%) occur frequently at the other two positions. Glycine enhances the stability by forming hydrogen bonds among the 3 chains. Collagen also contains two amino acids, hydroxyproline and hydroxylysine (1.3%), not often found in other proteins [32].

The first stage in the synthesis of collagen is the formation inside the cell of mRNA for each type of the polypeptide alpha-chain. The polypeptide alpha-chains

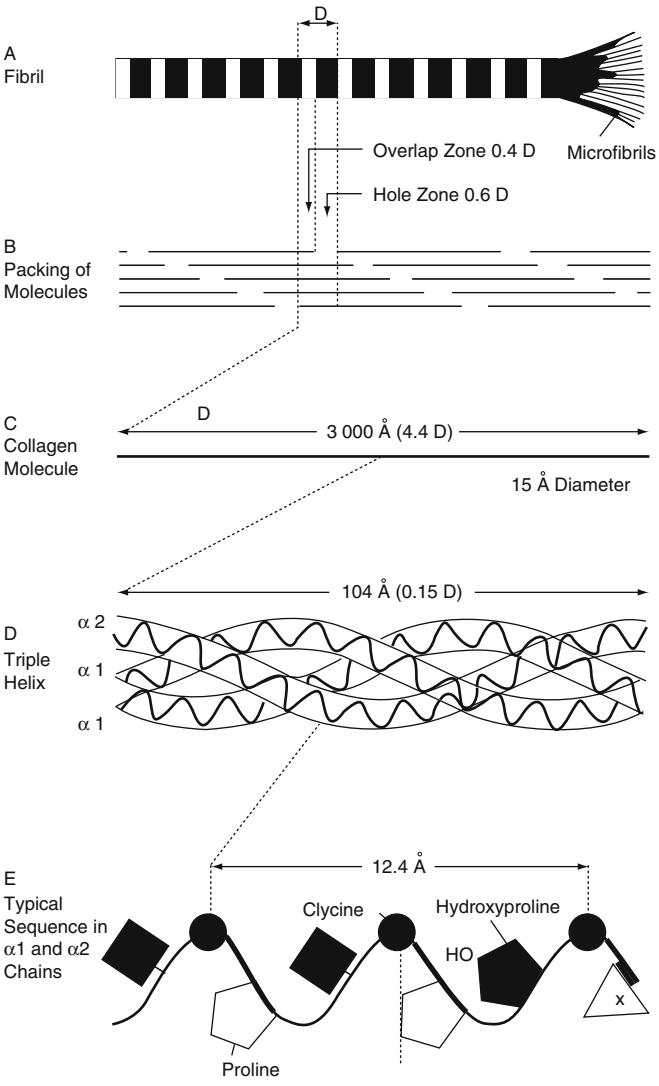

FIGURE 1-11. Tropocollagen.

assemble on the polyribosomes that are bound to the membranes of the rough endoplasmic reticulum. They are then injected into the cisternae as preprocollagen molecules. The signal peptide is clipped off, forming procollagen. About half the proline and some lysine are hydroxylated inside the tenoblast, just before the chains twist into the triple helix to form procollagen. The enzymes that mediate this require iron and vitamin C as cofactors.

Hydroxyproline is involved in the hydrogen bonding between the polypeptide chains, while hydroxylysine is involved in the covalent crosslinking of tropocollagen into bundles of various sizes. Both these amino acids increase the strength of collagen. In vitamin C deficiency, there is an excessive amount of hydroxyproline in the urine, and the collagen is defective. At both ends of procollagen there are nonhelical peptides, the domains. When procollagen leaves the cell, the domains are cleaved enzymatically by peptides to form tropocollagen. The adjacent molecules of collagen pack together overlapping by a quarter stagger, and appear as cross-striations under an electron microscope [38].

Crosslinks

Tropocollagen molecules are stabilized and held together by electrostatic, crosslinking chemical bonds. Hydroxyproline is involved in hydrogen bonding (intramolecularly) between the polypeptide chains. Hydroxylysine is involved in covalent (intermolecularly) crosslinking between adjacent tropocollagen molecules [39]. Both increase the strength of collagen, and the crosslinks result

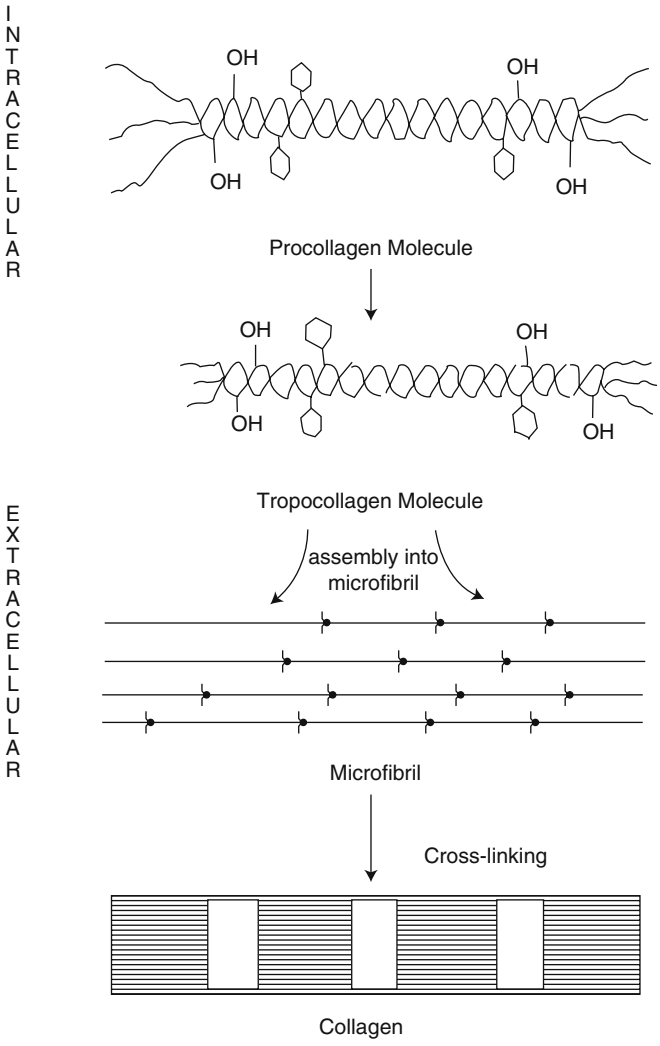

FIGURE 1-12. Production of Collagen.

from enzyme-mediated reactions, mainly lysine and hydrolysine. The key enzyme is lysyl-oxidase, which is the rate-limiting step for collagen crosslinking.

Hydroxylysins containing crosslinks are the most prevalent intermolecular crosslinks in native insoluble collagen. Crosslinks are important to the tensile strength of collagen, allow increased energy absorption, and increase its resistance to proteases.

Collagen fibers acquire all the crosslinks they will have shortly after synthesis. Crosslinks are at the maximum in early postnatal life and reach their minimum at physical maturity. Newly synthesised collagen molecules are stabilized by reducible crosslinks, but their numbers decrease during maturation. Nonreducible crosslinks are found in mature collagen, which is a stiffer, stronger, and more stable. Reduction of crosslinks results in extremely weak, friable collagen fiber. Crosslinking of collagen is one of the best biomarkers of aging.

Crosslinking substances are produced as charged groups, and they are removed by metabolic processes in early life but accumulate in old age, e.g. hydroxyproline is released quickly and in large quantities in young animals, but it is released more slowly and in smaller amounts in older animals.

Elastin

Elastin contributes to the flexibility of a tendon. This protein does not contain much hydroxyproline or lysine, but is rich in glycine and proline. It has a large content of valine and contains desmosine and isodesmonine, which form crosslinks between the polypeptides, but no hydroxylysine. Elastin does not form helices and is hydrophobic. Elastin is usually less than 1 μm in length, has no periodicity and requires special staining. Very little elastin is found in healing wounds.

Cells

The cell types in tendons are tenocytes and tenoblasts or fibroblasts. Tenocytes are flat, tapered cells, spindle-shaped longitudinally and stellate in cross section. Tenocytes lie sparingly in rows between collagen fibrils [35]. They have elaborate cell processes that form a three-dimensional network extending through the extracellular matrix. They communicate via cell processes and may be motile [40,41]. Tenoblasts are spindle-shaped or stellate cells with long, tapering, eosinophilic flat nuclei. Tenoblasts are motile and highly proliferative. They have well-developed, rough endoplasmic reticulum, on which the precursor polypeptides of collagen, elastin, proteoglycans, and glycoproteins are synthesized [32]. Tendon fibroblasts (tenoblasts) in the same tendon may have different functions. The epitenocyte functions as a modified fibroblast with well-developed capacity of repair.

Ground Substance

Ground substance is a complex mixture of proteoglycans and glycoproteins surrounding the collagen fibers. It has a high viscosity that provides the structural support, lubrication, and spacing of the fibers essential for gliding and cross-tissue interactions. The ground substance is a medium for the diffusion of nutriments and gases, and regulates the extracellular assembly of procollagen into mature collagen. Water makes up 60% to 80% of the total weight of the ground substance. Proteoglycans and glycoproteins in the ground substance account for less than 1% of the total dry weight of tendon. They maintain the water within the tissues and are involved with intermolecular and cellular interactions. Proteoglycans and glycoproteins also play an important role in the formation of fibrils and fibers. The covalent crosslinks between the tropocollagen molecules reinforce the fibrillar structure.

The water-binding capacity of these macromolecules is important. Most proteoglycans are oriented at 90 degrees to collagen, and each molecule of proteoglycans can interact with 4 collagen molecules. Others are randomly arranged to lie parallel to the fibers, but they interact only with that fiber [42]. The matrix is constantly being turned over and remodeled by the fibroblasts and by degrading enzymes (collagenases, proteoglycanase, glycosaminoglycanase, and other proteases).

The proteogylcans and glycoproteins consist of two components, glycosaminoglycans (GAGs) and structural glycoproteins. The main proteogylcans in tendons associated with glycosaminoglycans are dermatan sulfate, hyaluronic sulfates, chondroitin 4 sulfates, and chondroitin 6 sulfates. Other proteoglycans found in tendons include biglycan, decorin, and aggrecan. Aggrecan is a chondroitin sulfate bearing large proteoglycan in the tensional regions of tendons [43]. The glycoproteins consist mainly of proteins, such as fibronectin, to which carbohydrates are attached.

Fibronectins are high-molecular-weight, noncollagenous extracellular glycocoproteins. Fibronectin plays a role in cellular adhesion (cell-to-cell and cell-to-substrate) and in cell migration. Fibronectin may be essential for the organization of collagen I and III fibrils into bundles, and may act as a template for collagen fiber formation during the remodeling phase.

Hyaluronate is a high-molecular-weight matrix glycosaminoglycan, which interacts with fibronectin to create a scaffold for cell migration. It later replaces fibronectin.

Integrins are extracellular matrix binding proteins with specific cell surface receptors. Large amounts of aggrecan and biglycan develop at points where tendons wrap around bone and are subjected to compressive and tensional loads. TGF-beta could be involved in differentia-

tion of regions of tendon subjected to compression, because compressed tendon contains both decorin and biglycan, whereas tensional tendons contain primarily decorin [44].

The synthesis of proteoglycans begins in the rough endoplasmic reticulum, where the protein portion is synthesized. Glycosylation starts in the rough endoplasmic reticulum and is completed in the Golgi complex, where sulfation takes place. The turnover of proteoglycans is rapid, from 2 to 10 days. Lysosomal enzymes degrade the proteoglycans, and lack of specific hydrolases in the lysososmes results in their accumulation.

When newly formed, the ground matrix appears vacuolated. The formation of tropocollagen and extracellular matrix are closely interrelated. The proteoglycans in the ground substance seem to regulate fibril formation as the content of proteoglycans decreases in tendons when the tropocollagen has reached its ultimate size. An adequate amount of ground substance is necessary for the aggregation of collagenous proteins into the shape of fibrils.

Crimp

Collagen fibrils in the rested, nonstrained state are not straight but wavy or crimped. Crimp represents a regular sinusoidal pattern in the matrix. Crimp is a feature of both tendons and ligaments. The periodicity and amplitude of crimp is structure specific [45]. It is best evaluated under polarized light. Crimp provides a buffer in which slight longitudinal elongation can occur without fibrous damage, and acts as a shock absorber along the length of the tissue. Different patterns of crimping exist: straight, or undulated in a planar wave pattern.

Collagen production can be affected by many factors. These include: heredity, diet, nerve supply, inborn errors, and hormones. Corticosteroids are catabolic, and they also inhibit the production of new collagen. Insulin, estrogen and testosterone can actually increase the production of collagen.

Disorders of collagen include osteogenesis imperfecta, Ehlers-Danlos, scurvy, and progressive systemic sclerosis. Muscles and tendons atrophy and the collagen content decreases when the nerve supply to the tendon is interrupted. Inactivity also results in increased collagen degradation, decreased tensile strength, and decreased concentration of metabolic enzymes. Due to the reduction of enzymes that are essential for the formation of collagen with age, repair of soft tissue is delayed in the older age groups. Exercise increases collagen synthesis, the number and size of the fibrils, and the concentration of metabolic enzymes. Physical training increases the tensile and maximum static strength of tendons.

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2
Mechanical Properties of Tendons

Constantinos N. Maganaris and Marco V. Narici

The primary role of tendons is to transmit contractile forces to the skeleton to generate joint movement. In doing so, however, tendons do not behave as rigid bodies. In this chapter, the mechanical behavior of tendons and its major determinants and implications are reviewed.

In Vitro Measurements

Most of our knowledge of the mechanical properties of tendons comes from isolated material testing. Two methods have traditionally been used in biomechanics investigations: 1) The free-vibration method, which is based on quantifying the decay in oscillation amplitude that takes place after a transient load is applied to a specimen [1–3]; and 2) tensile testing methodologies, in which the specimen is stretched by an external force while both the specimen deformation and the applied force are recorded [2,4–6]. The latter methodology seems to be preferable, mostly because it is considered to mimic adequately the way that loading is imposed on tendons in real life [7–14].

A tensile testing machine is composed of an oscillating actuator and a load cell (see Figure 2-1). The tendon specimen studied is gripped by two clamps, a static one mounted on the load cell and a moving one mounted on the actuator. The actuator is then set to motion while the load cell records the tension associated with the stretching applied. The tensile deformation of the specimen is taken from the displacement of the actuator, in which case the deformation of the whole specimen is quantified, or by means of an extensometer, in which case deformation measurements are taken over a restricted region of the whole specimen.

A typical force-deformation plot of an isolated tendon is shown in Figure 2-2. Generally, in force-deformation curves, slopes relate to stiffness (N/mm), and areas to energy (J). In elongation-to-failure conditions, 4 different regions can be identified in the tendon force-deformation curve. Region I is the initial concave portion of the curve, in which stiffness gradually increases; it is referred to as the tendon "toe" region. Loads within the toe region elongate the tendon by reducing the crimp angle of the collagen fibers at rest, but they do not cause further fiber stretching. Hence, loading within the toe region does not exceed the tendon elastic limit, and subsequent unloading restores the tendon to its initial length. Further elongation brings the tendon into the "linear" Region II, in which stiffness remains constant as a function of elongation. In this region, elongation is the result of stretching imposed in the already aligned fibers by the load imposed in the preceding toe region. At the end point of this region, some fibers start to fail. Thus, A) the tendon stiffness begins to drop; and B) unloading from this point does not restore the tendon's initial length. Elongation beyond the linear region brings the tendon into Region III, where additional fiber failure occurs in an unpredictable fashion. Further elongation brings the tendon into Region IV, where complete failure occurs [4,5,15–18].

Although Regions I, II, III, and IV are apparent in tendon force-deformation curves during elongation-to-failure conditions, the shape of the curves obtained differs between specimens. These differences can be accounted for to a great extent by interspecimen dimensional differences. For example, tendons of equal lengths but different cross-sectional areas exhibit different force-deformation properties, and thicker tendons are stiffer. Similarly, different force-deformation curves are obtained from tendons of equal cross-sectional areas but different initial lengths, in which case shorter tendons are stiffer [5].

To account for interspecimen dimensional differences, tendon force is reduced to stress (MPa) by normalization to the tendon cross-sectional area, and tendon deformation is reduced to strain (%) by normalization to the tendon original length. The tendon stress-strain curve is similar in shape to the force-deformation curve, but it

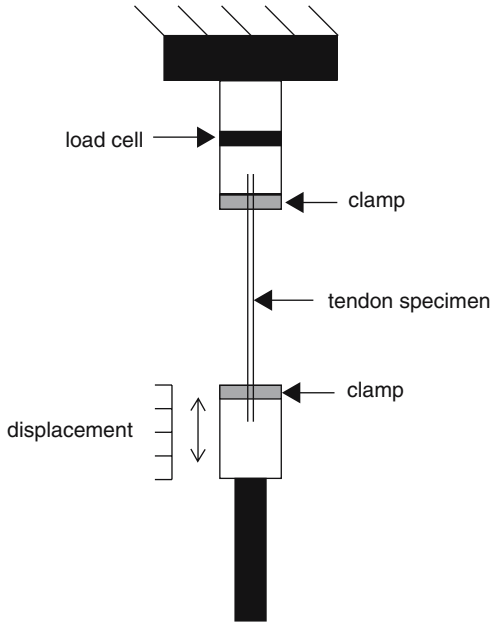

FIGURE 2-1. Diagram of an apparatus for tendon tensile testing.

reflects the intrinsic material properties rather than the structural properties of the specimen.

The most common material variables taken from a stress-strain curve under elongation-to-failure conditions are Young's modulus (GPa), ultimate stress (MPa), ultimate strain (%), and toughness (J/kg). Young's modulus is the product of stiffness multiplied by the original length-to-cross-sectional area ratio of the specimen. Experiments on several tendons indicate that the Young's modulus reaches the level of 1 to 2 GPa at stresses exceeding 30 MPa [5,11,12,19]. Ultimate tendon stress (i.e., stress at failure) values in the range of 50 to 100 MPa are generally reported [5,11,12,17]. Ultimate tendon strain (i.e., strain at failure) values of 4% to 10% have been reported [5,16,17]. The tendon toughness (i.e., work done on the tendon until failure) values reported are in the range of 1000 to 4500 J/kg [12].

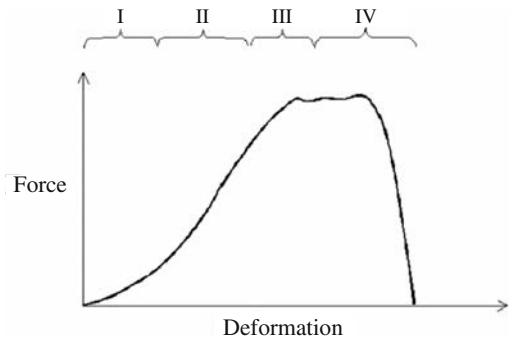

FIGURE 2-2. Typical force-elongation curve of a tendon pulled by a load exceeding the tendon elastic limit. I, toe region; II, linear region; III and IV, failure regions.

If a tendon is subjected to a tensile load, the tendon does not behave perfectly elastically, even if the load applied is less than that required to cause failure. This is because the tendon collagen fibers and interfiber matrix possess viscous properties [20,21]. Due to the presence of viscosity, the entire tendon exhibits force-relaxation, creep, and mechanical hysteresis [2,4,5,8,15,16,22].

Force-relaxation means that the force required to cause a given elongation decreases over time. The decrease in force follows a predictable curvilinear pattern until a steady-state value is achieved (see Figure 2-3). Creep is the analogous phenomenon under constant-force conditions. In this case, deformation increases over time curvilinearly until a steady state value is reached. In both force-relaxation and creep, the decrease in magnitude of

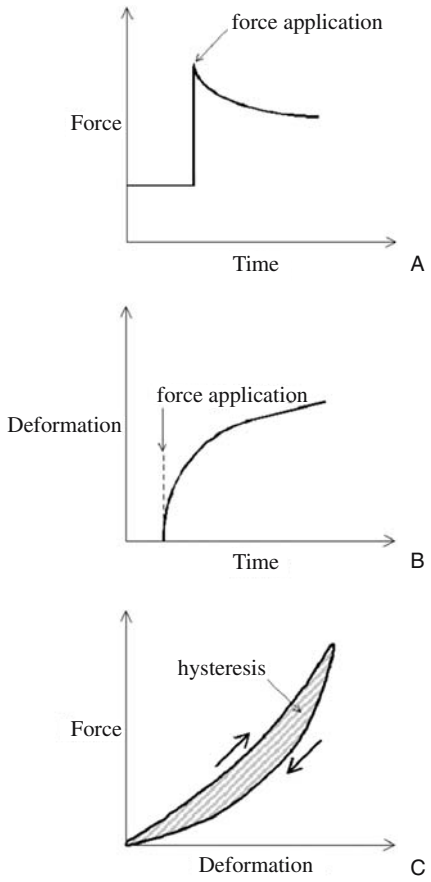

FIGURE 2-3. (A) Typical force-relaxation curve in a tendon. The force required to cause a given deformation decreases over time. (B) Typical creep curve in a tendon. The deformation caused by a given force increases over time. (C) Typical mechanical hysteresis in a tendon. The arrows indicate loading and unloading directions during a test with a tensile load within the elastic limit of the tendon. The area of the loop between the loading and unloading curves relative to that underneath the loading curve represents the fraction of strain energy lost as heat by the tendon viscous damping.

the variable studied reflects the viscous component of the tendon, and the steady-state values reflect the elastic component of the tendon. The presence of mechanical hysteresis is retrieved in load-deformation plots during loading and subsequent unloading of the specimen [2,6,8,12]. Larger tendon deformations are taken during recoil than stretch at given loads, yielding a loop (the hysteresis loop) between the curves in the loading and unloading directions (see Figure 2-3). The area of the loop represents the amount of strain energy lost as heat upon recoil due to the viscous component, and it is usually expressed in relative terms (%) with respect to the total work performed on the tendon during stretching. Mechanical hysteresis values in the range of 5% to 25% have been reported, with most values concentrated around the value of 10% [7,8,11,12,19]. The proportion of strain energy input recovered by elastic recoil is the converse of mechanical hysteresis, and is known as rebound resilience. This variable is, therefore, an index of the material potential for elastic energy recovery.

Several factors may account for differences in the material properties of tendons. Some differences can be attributed to interstudy methodological differences in A) tendon gripping (conventional clamps, Cryo Jaw clamps, or use of cyanoacrylate adhesive [2,6,8,11,12,23]; B) tendon deformation measurement (actuator-based measurements, extensometer-based measurements, or noncontact optical methodologies [2,6,9,11,24]; and C) tendon cross-sectional area measurement (gravimetry-based measurements, micrometry-based measurements, or mass- and density-based estimations [9,11,25]. Some studies have shown that the status of the specimen studied (e.g., preserved or fresh) and the environmental conditions during testing may also affect the mechanical response of collagenous tissue [5,26–28], thus accounting for the above variations.

Studies on the effect of several other factors on the mechanical properties of tendinous tissue have been performed. The major of these factors are discussed below.

Disuse

To determine the effects of disuse on tendinous tissue properties, 3 limb immobilization models have traditionally been employed. In most experiments, the joint is fixed at a certain position for a prolonged period of time. Using the specimens of the contralateral, nonimmobilized limb as controls, postintervention comparisons are then made [5,10,29,30]. Limb suspension and denervation models have also been used [29,31]. Most studies show that immobilization results in decreased stiffness, ultimate strength and energy-to-failure. These changes are attributed to specimen atrophy and changes in the specimen material properties. Disuse-induced changes in intrinsic material properties are associated with increased collagen turnover and reducible cross-linking, decreased glycosaminoglycan and water content, and increased nonuniform orientation of collagen fibrils [5,10,17,18, 31–33].

Physical Activity

Most of the studies report that long-term physical activity improves the tensile mechanical properties of tendons and yields opposite effects compared with disuse [5,9,10,30,34]. Increases in stiffness, ultimate strength, and energy-to-failure in response to exercise training have been reported. Dimensional changes (i.e., hypertrophy) may partly account for these changes. Increases in ultimate stress and strain, however, indicate that the improvement of mechanical properties is also associated with training-induced changes in the tendon intrinsic material properties. Such biochemical and structural changes include increased glycosaminoglycan content, decreased collagen, reducible cross-linking, and increased alignment of collagen fibers [5,10,17,18,31–33].

Anatomical Site

Since chronic physical activity enhances the mechanical properties of tendons, it would be reasonable to suggest that tendons located at anatomical sites that allow high-level and frequent loading may have enhanced properties as compared with tendons loaded by low-level forces. Examples of tendons that are frequently loaded by high-tensile loads are the tendons of the ankle plantarflexor and digital flexor muscles. These tendons are loaded by the ground impact forces during terrestrial locomotion. At the other end of the spectrum are the tendons of the ankle dorsiflexor and digital extensor muscles. These tendons are physiologically loaded primarily by the in-series muscles that contract to enable joint displacement. Some experimental results indicate that the location and functional role of a tendon may be associated with the tendon mechanical response [12,35], but more recent studies stand in opposition with the above notion [19,36].

Aging

Several studies have shown that aging affects the properties of tendinous tissue [4,5,12,15,18,37,38]. However, some studies have shown that aging may result in intrinsically stiffer, stronger, and more resilient tendons [12,13], while other studies have challenged these results [37–40]. This inconsistency may be partly accounted for by differences in the initial age examined. In some studies, specimens from very young subjects have been used [12,35,41]. On such occasions, changes in tissue properties reflect changes occurring as a function of maturation, which may mask an actual aging effect.

Steroids

Corticosteroids have frequently been used for the treatment of articular inflammations. Intra-articular and intracollagenous injections of corticosteroid may reduce the stiffness, ultimate stress, and energy-to-failure of collagenous tissue, even after short-term administration [42–44]. These results indicate that steroids may predispose the user to tendon injuries. Furthermore, using steroids may also impair the tendon healing process after an injury [45].

In Situ and *In Vivo* Protocols

In vitro–based studies have made it clear that tendons do not behave as rigid elements. Reference, however, to mechanical properties of *in vitro* material when interpreting *in vivo* function should be treated with caution. Although frequencies met in physiological locomotion have often been used in *in vitro* tensile tests, three important facts raise doubts as to whether such tests can mimic or predict accurately the tendon mechanical behavior under *in vivo* loading conditions: 1) Fixing a fibrous structure with clamps is inevitably associated with A) slippage of the outer fibers; and B) stress concentration that may result in premature fracture. 2) Many experiments have been performed using preserved tendons, which may have altered properties [26,27]. 3) Tendon loads within the physiological region have traditionally been predicted from the muscle maximal stress potential, which has been treated as a constant [12,25,46]. There is experimental evidence, however, that maximal muscle stress is muscle-specific, with fiber composition being the major determinant factor [47–49].

Some of these problems have been circumvented by testing animal tendons *in situ* after the animal has been killed or anesthetized [50–53]. This has been achieved by surgically releasing the tendon from its surrounding tissues, maintaining the proximal end of the tendon attached to the in-series muscle, and having the distal bone of the muscle-tendon unit gripped by a clamp interfaced to a load cell. The *in situ* muscle contracts artificially by electrical stimulation and pulls the tendon, which lengthens as a function of the contractile force applied to its proximal end in a similar fashion to that obtained when the actuator of a tensile machine pulls an isolated specimen (see Figure 2-4). The advantage of such experimental protocols is that they allow assessment of the tendon and aponeurosis (i.e., intramuscular tendon) mechanical properties A) separately, and B) under physiological loading levels. Notwithstanding these advantages, the above *in situ* protocols are not applicable to humans. However, adapting similar principles to those used under *in situ* material testing has recently allowed

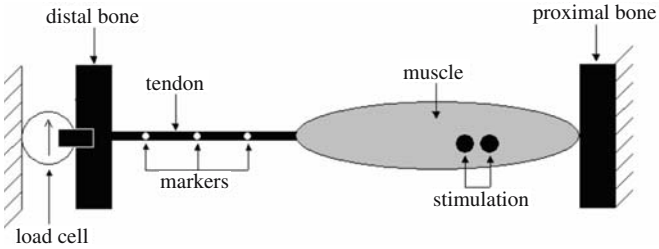

FIGURE 2-4. Experimental set-up to measure the mechanical properties of a tendon *in situ*. The muscle-tendon complex is intact. The proximal and distal bones are clamped. Loading is imposed by stimulation-induced muscle contraction. The resultant forces are measured by a load cell placed in series with the muscle-tendon complex. The resultant deformation in the tendon is obtained from off-line analysis of the displacement of markers attached on the tendon.

the development of a noninvasive method for assessing the mechanical properties of human tendons *in vivo*.

The method is based on real-time, sagittal-plane ultrasound scanning of a reference point along the tendon during static contraction of the in-series muscle. The limb is fixed on the load cell of a dynamometer to record changes in muscle torque during isometric contraction (see Figure 2-5). The tensile forces generated by contrac-

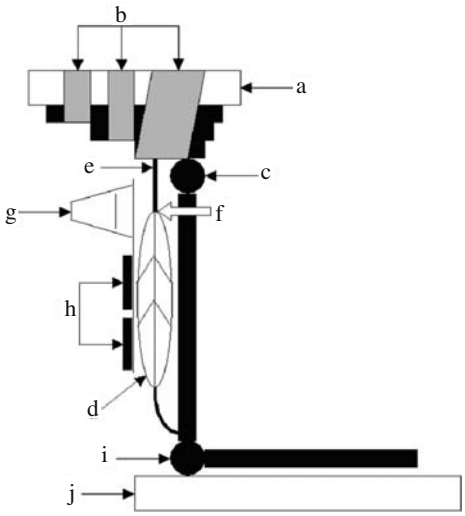

FIGURE 2-5. Experimental set-up to measure the mechanical properties of the human tibialis anterior tendon *in vivo*. The limb is fixed on the footplate of a dynamometer. Isometric muscle contractions are generated by stimulation, while the resultant displacement of the myotendinous junction is recorded in real time using ultrasonography. The load imposed is taken from the dynamometer reading. a, dynamometer footplate; b, velcro straps; c, ankle joint; d, tibialis anterior muscle; e, tibialis anterior tendon; f, myotendinous junction; g, ultrasound probe, h; percutaneous stimulating electrodes; i, knee joint; j, knee mechanical stop. (Reprinted with permission from Maganaris and Paul.)

tion pull the tendon proximally and cause a deformation, which is measured by the recorded displacement of the reference landmark in the tendon (see Figure 2-6). The load-elongation plot obtained by this method resembles in form that taken using *in vitro* and *in situ* methodologies for muscle [36,54–56].

Particular attention should be paid at several stages in the measurements taken with the above *in vivo* method:

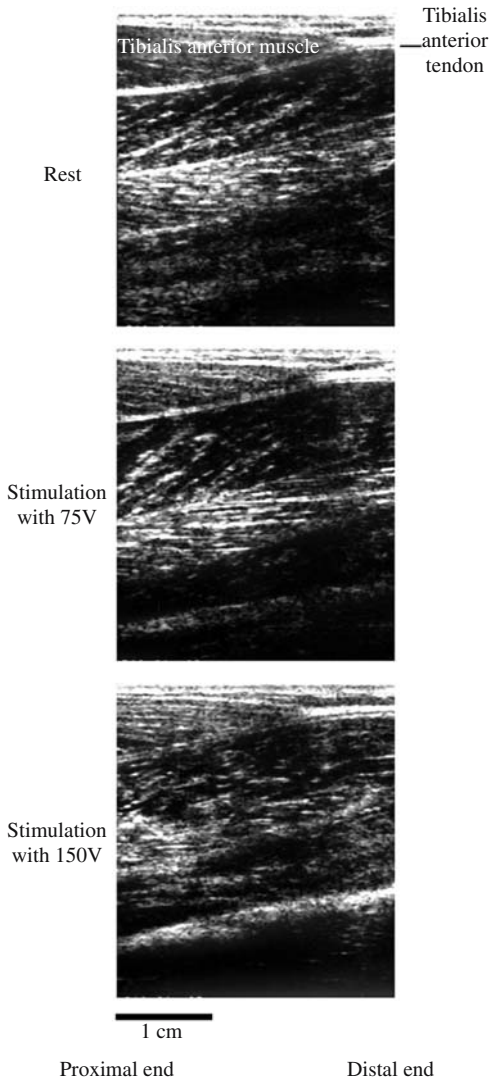

FIGURE 2-6. Ultrasound-based assessment of tendon elongation. The sonographs shown were taken over the tibialis anterior myotendinous junction of a subject at rest (top), and electrical stimulation of the tibialis anterior muscle at 75 V (middle) and 150 V (bottom). The white arrow in each scan points to the tibialis anterior tendon end in the myotendinous junction. Notice the displacement of this reference landmark in the transition from rest to 75 V contraction and from 75 to 150 V contraction. The displacements shown were digitized and combined with the respective estimated force applied in the tendon to calculate the tendon force-elongation relation [54].

1) A reference marker visible in all scans recorded throughout the entire contraction must be selected. We found that the tendon proximal end in the myotendinous junction is a reliable landmark. Since the tendon is echoreflective and the muscle echoabsorptive, the myotendinous junction can be seen clearly. Reproducibility measurements of the displacement of the tendon distal end in the myotendinous junction as assessed by ultrasonography have yielded intra- and interobserver coefficients of variation of less than 10% [54–57]. Other authors have used as reference markers the intersection points of fascicles in the aponeurosis of the muscle [58–62]. This approach has the disadvantage that it yields displacements not only in the tendon, but also in a part of the aponeurosis, which may have different mechanical properties than the tendon itself [52,53]. Moreover, it is practically impossible to retrieve the location of a given fascicle (and therefore a given reference landmark) once the scanning probe has been removed from the scanned limb.

2) The scanning probe must be fixed on the skin over the scanned limb [54,60–62], or an external constant point [36]. Adhesive tape has been shown to be effective in fixing the probe securely on the skin.

3) The method necessitates that the contraction of the muscle is truly isometric, i.e., no joint movement occurs. However, this is virtually impossible because A) structures surrounding the joint deform by the loading induced by contracting the muscle, e.g. ligaments, surrounding muscles and fat pads, and A) the dynamometer itself has an inherent compliance. Therefore, additional measurements need to be taken to correct for unwanted shifts in the tendon "fixed" end when the scanning probe is externally fixed [36]. Kinematic measurements of the joint angle studied during contraction can give an estimate of the shift in the tendon "fixed" end [61,62].

4) The contractile forces elicited must be transmitted entirely to the tendon. If other muscles co-contract, then the forces recorded by the dynamometer load cell do not represent the tensile load applied to the tendon. Several authors, however, have neglected this important effect [58–62]. Isolating the mechanical action of a muscle can be achieved through percutaneous electrical stimulation over the muscle's motor points or main nerve branch [54–56].

5) To reduce force to stress and elongation to strain, the tendon initial dimensions are required. These can also be taken using ultrasonography [54,55,58]. To obtain the mechanical hysteresis of the tendon, the contracting muscle must relax to allow the tendon to recoil [56].

By following the above steps, we estimated the mechanical properties of the human tibialis anterior and

gastrocnemius tendons. The tendon Young's modulus and mechanical hysteresis values obtained were ~1.2 GPa and 18%, respectively [36,54–56]. Notwithstanding the good agreement of these estimates with *in vitro* tendon experimental results, the *in vivo* experiments failed to show the tendon linear region. Instead, the tendon tensile response was curvilinear over the loads examined. This finding indicates that isometric contractions of the tibialis anterior and gastrocnemius tendons generate tendon loads within the toe region, and are therefore unlikely to tear the tendon in a single pull. Further tensile measurements with reference landmarks chosen along the aponeurotic part of the tibialis anterior tendon showed that A) the entire aponeurosis strains almost 3 times as much as the tendon and B) the aponeurosis's strain is not homogeneous along its entire length [55,57]. Moreover, morphometric analysis of scans taken in the axial plane of the muscle showed that contraction increases the resting-state aponeurosis's width and entire area [63]. These *in vivo* findings are in line with *in situ*–based reports [52,53,64].

The general consistency between the above *in vivo* findings and *in situ*-based results, as well as results from measurements on *in vitro* material subjected to tensile loads much smaller than that required to cause failure, adds credibility to the *in vivo* method. However, further studies are required to eliminate potential measurement errors. Although anatomical measurements on cadaveric muscle-tendon units have indicated that ultrasonography accurately locates connective tissue at rest [65,66], systematic research is needed to assess the accuracy of ultrasound-based measurements of connective tissue dimensions during movement upon muscle contraction and subsequent relaxation. Clearly, however, future research with respect to *in vivo* protocols should also be focused on quantifying the errors made in the measurement/calculation of tendon load.

Functional Consequences of the Mechanical Behavior of Tendons

The elasticity exhibited by a tendon on application of a tensile load has several important implications for the function of the in-series muscle.

First, having a muscle attached to a compliant tendon makes it more difficult to control the position of the joint spanned by the tendon [67]. Consider, for example, an external oscillating force applied to a joint at a certain angle. Trying to maintain the joint still would require generating a constant contractile force in the muscle. If the tendon of the muscle is very compliant, its length will change by the external oscillating load, even if the muscle is held at a constant length. This will result in failure to maintain the joint at the angle desired.

Second, the elongation of a tendon during a static muscle contraction is accompanied by an equivalent shortening in the muscle. For a given contractile force, a more extensible tendon will allow greater shortening of the muscle. This extra shortening induces shortening in the sarcomeres of the muscle. According to the cross-bridge mechanism of contraction [68], the result of this sarcomeric shortening on the contractile force elicited would depend on the region over which the average sarcomere of the muscle operates. If the sarcomeres operate in the ascending limb of the force-length relation, a more extensible tendon will result in less contractile force. In contrast, if the sarcomeres operate in the descending limb of the force-length relation, having a more extensible tendon will result in greater contractile force [51,69].

Third, stretching a tendon results in elastic energy storage. Since tendons exhibit low mechanical hysteresis, most of the elastic energy stored during stretching is returned once the tensile load is removed. This passive mechanism of energy provision operates in tendons in the feet of legged mammals during terrestrial locomotion, thus saving metabolic energy that would otherwise be needed to displace the body ahead [36,70,71].

The interplay between the mechanical properties of tendons and muscle function necessitates full appreciation of the mechanical properties of a healthy tendon when aiming at restoring normal muscle function and joint performance. Consider, for example, surgical procedures involving limb and muscle-tendon lengthening. Any change in the resting-state length of the tendon without taking into account that this will change the extensibility of the tendon itself will clearly affect the function of the in-series muscle. Therefore, protocols for the assessment of the mechanical properties of tendons *in vivo* could provide crucial help for optimizing the outcome of a corrective surgery. For example, they could be used for measurements in the tendon of the contralateral healthy limb of the patient, thus providing reference values that could then be used for guiding the decision making.

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3
Growth and Development of Tendons

Laurence E. Dahners

Introduction

Tendons appear in the mesenchyme of the limb bud at 6 to 8 weeks of fetal life and join with the muscles originating from the somites. They are initially very cellular but become less so throughout growth to adulthood as matrix elements are synthesized. Their collagen fibrils become larger in diameter during maturation while the tendons are also gaining in cross section. Longitudinal growth is diffuse, rather than occurring at a growth plate as in bone, and the mechanism of this growth appears to involve the sliding of collagen fibers or fibrils past one another.

Fetal Formation

Tenocytes originate from the somatopleure which differentiates into the mesenchyme that forms the embryonic limb bud. The subsequent development of the tendons requires the presence of muscle tissue originating in the somites. If the somites are destroyed by radiation, tendon development ceases [1].

For the most part, fetal tendons consist of Type I and Type III collagen fibrils, proteoglycans, and tenocytes (fibroblasts). Fetal collagen fibrils are small in diameter (10 to 30 nm). Fetal tendon is very cellular as compared to mature tendon, having as many as 200 000 cells per mm^3. Between 6.5 and 8 weeks into the development of the embryo, tendons can be first detected at the ends of the fetal muscle bellies. Upper extremity tendons develop more rapidly than lower extremity tendons, and flexor tendons develop more rapidly than extensor tendons.

Changes During Postnatal Growth

Changes in Cellularity

At birth tendons are highly cellular, having 200 000 cells per mm^3. The cellularity drops rapidly during the first five years of life to approximately 100 000 cells per mm^3. The cellularity continues dropping, reaching about 50 000 cells per mm^3 by age 15 to 20 [2]. The cellularity is so high that in newborns the cell-to-matrix ratio appears to be one-to-one [3]. During growth, as the cellularity decreases, the tenoblasts become tenocytes. They become longer and more slender, and their cytoplasmic processes elongate, forming a dense network around and through the surrounding collagenous matrix. As the tendon matures, there is a decrease in the numbers of the intracellular organelles responsible for protein synthesis [4].

Changes in the Matrix

With the decrease in cellularity of the growing tendon, it is obvious that there is relative increase in the amount of matrix. Collagen fibril diameters increase during growth. In the fetus and the newborn, most fibrils are 40 nm in diameter or smaller, whereas in more mature tendons much larger diameters are represented, ranging up to 500 or even 600 nm [5]. With growth there is no increase in the number of elastic fibers contained within the tendon. Water content drops from 75% in the newborn to 61% in the young animal, and mucopolysaccharide content drops as well.

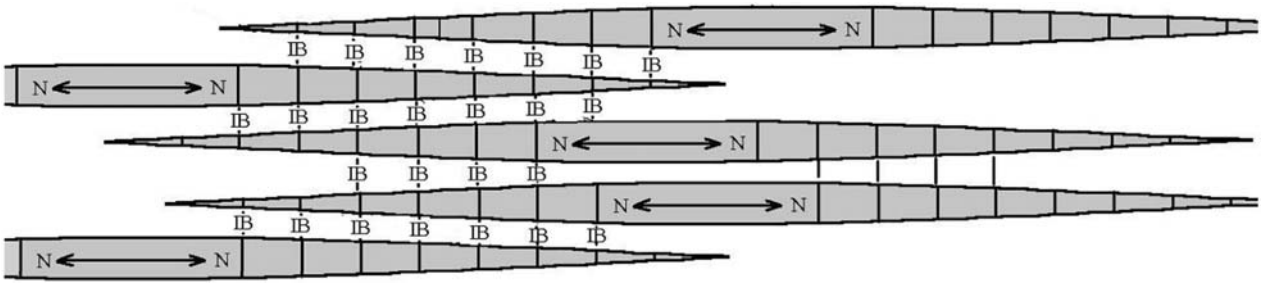

FIGURE 3-1. Collagen fibrils are represented here in gray. They taper to points on both ends, and the ends are apparently mostly amino terminal. These are not drawn to scale, as collagen fibrils in rat are 300 to 500 times as long as their radius. "IB" represents the presumed interfibrillar bonds, which are thought to be temporarily released to allow fibril sliding during elongation of the tendon during growth.

Cross-Sectional Growth

The cross-sectional area of tendon increases in a relatively linear fashion from birth through puberty. At birth, the tendon of the biceps brachii has a cross-sectional area of about 8 mm^2 and the area increases linearly, reaching approximately 37 mm^2 by age 20, when the growth curve flattens out [6]. In ligament, there is evidence that much of the new tissue formed to increase diameter is laid down by surface cells (so-called "periligament") [7], and it seems likely that a similar mechanism is involved in increasing the diameter of tendons.

Longitudinal Growth

Marker studies using sutures in growing animals have demonstrated that longitudinal growth occurs interstitially throughout the length of tendons rather than at a "growth plate" or area as occurs in bone. While Crawford [8] found increased growth at the muscle-tendon junction in rabbits, Nishijima et al. [9,10] did not find this phenomenon in their studies of the rabbit or chicken muscle tendon junction. Nishijima felt that longitudinal tendon growth in an area corresponded to the amount of growth in the underlying bone. Such diffuse interstitial growth most likely occurs through the sliding of fibrils or bundles of fibrils past one another. As they slide so that they overlap less, the tendon is lengthened. This presumably occurs through the release of reversible interfibrillar bonds with their reattachment after the fibrils have finished sliding (see Figure 3-1). These reversible interfibrillar bonds have been postulated to involve the decorin molecules which "decorate" the surface of collagen fibrils. NKISK, a competitive inhibitor of the binding of decorin to fibronectin (a molecule which frequently fills the role of tissue adhesive) has been shown to potentiate creep in rat tail tendons. Tendons that have been stretched in the presence of NKISK have been demonstrated to undergo sliding of fibrils or bundles of fibrils [11]. Such sliding of fibrils has been documented *in vivo* in growing and in contracting ligaments, but not in tendon [12].

Fetal Tendon Tissue Response to Injury

Fetal tissue in the early to mid-gestational stage responds to injury in a fundamentally different manner than does adult tissue. In general, fetal wound healing occurs at a faster rate and in the absence of scar formation [13]. Fetal tendon tissue undergoes scarless, regenerative healing [14]. The basis for the ability of fetal tissues to heal without scarring remains unknown. The regenerative response of fetal tissues is intrinsic to the tissues themselves, not of the fetal environment [15]. It is therefore possible that biologic modulation of tendon tissue repair potentially could lead to a regenerative healing process in adults [16,17], but the application of these ideas in clinical practice is still in the future.

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4
Aging and Degeneration of Tendons

Pekka Kannus, Mika Paavola, and László Józsa

Introduction: Aging

The process of aging is a universal, decremental, and intrinsic process which should be considered innate to our genetic design—not pathological [1]. The rate of aging is highly individual and depends on many factors, including genetics, lifestyle, and former disease processes [2].

Overuse tendinopathies are common in primary care. These tendon problems are not restricted to competitive athletes but affect recreational sports participants and many working people. The pathology underlying these conditions is usually tendinosis or collagen degeneration [3]. Kannus and coworkers [4] showed in a 3-year prospective controlled study that sports injuries in elderly athletes are more frequently overuse-related than acute and commonly have a degenerative basis.

The degenerative changes associated with increasing age may be detected as early as the third decade, when a progressive decline becomes apparent in cellular function in many tissues [5]. With aging, various functions of the body gradually deteriorate. This also includes the musculoskeletal system, even if not so extensively as the cardiovascular system [6]. The tendon is subjected to early degenerative changes, since both the collagen and noncollagenous matrix components of tendons show qualitative and quantitative changes. There are also many cellular and vascular changes within the aging tendon. However, in adults, studies have not found a clear correlation between macroscopic tendon characteristics, such as thickness and surface area, and age [7,8].

As a result of all these physiological age-related changes, an aged tendon is weaker than its younger counterpart, and is more likely to tear or suffer from overuse injury [9,10]. This is especially true if the aging tendon also suffers from pathological degenerative changes [11].

Cellular Changes

Many changes occur at the cellular level in an aging tendon. The tenoblasts transform into tenocytes (and occasionally vice versa) [11]. The volume density of tendon cells as well as the number of tendon cells per unit of surface area decrease. There is also a decrease in the plasmalemmal surface density. The tendon cells become longer, more slender, and more uniform in shape [12,13]. With age, the nucleus-to-cytoplasm ratio increases, and finally the main body of the cell is almost completely occupied by a long, thin nucleus [1] (see Figure 4-1).

The overall metabolic activity of tenoblasts decreases with age, most likely slowing the reparative ability of a tendon. There is a decline in the organelles participating in protein synthesis, particularly the rough endoplasmic retinaculum. Therefore, the ability to synthesize protein and amino acids decreases [12,14]. However, the rough endoplasmic retinaculum and Golgi apparatus can be still recognized at electron microscopy. The cytoplasm has high quantities of free ribosomes and the number of mitochondria is decreased, but they still have well-defined cristae. Lysosomes can be identified in varying numbers. With increasing age, and especially in pathologic conditions, tenocytes show increasing numbers and amounts of glycogen particles, lipid droplets, lipofuscin, and lysosomes [11]. Also, the metabolic pathways used to produce energy shift from aerobic to more anaerobic, and eventually some metabolic pathways such as the Krebs cycle completely shut down [11,15]. Reduced metabolic activity of the aged tendon has been recently shown in an *in vitro* model of a rat patellar tendon [16].

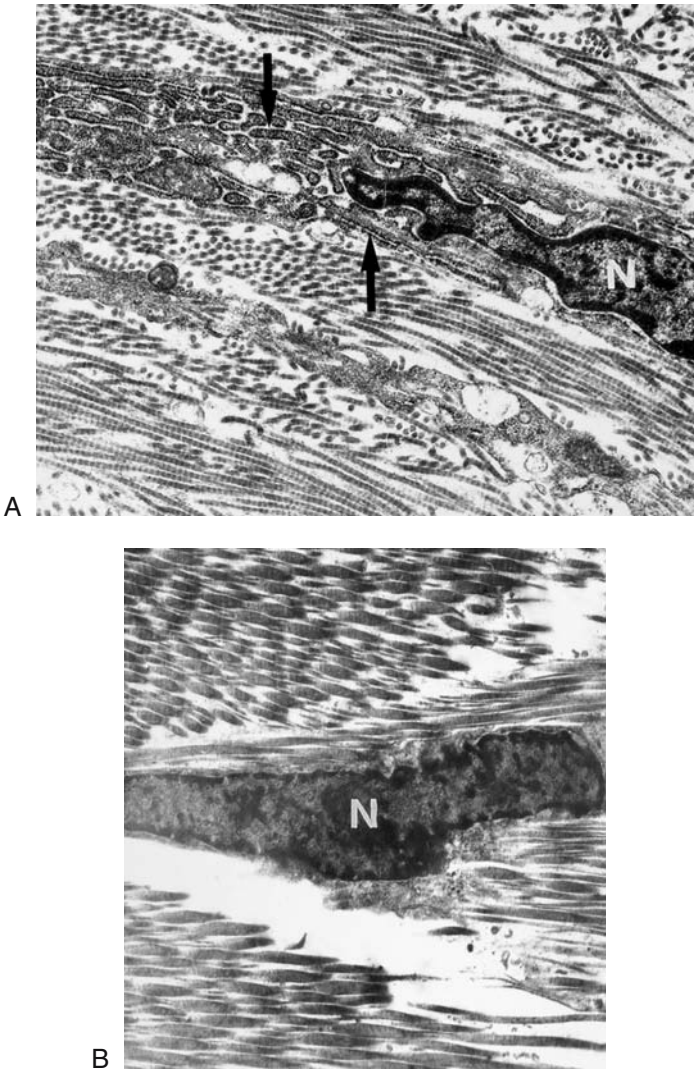

FIGURE 4-1. (A) A tenoblast with a well-developed, rough endoplasmic reticulum (arrows). N = nucleus. An intact Achilles tendon from a young adult cadaver (Transmission electron micrograph, TEM × 6600). (B) A tenocyte with a large nucleus (N) and high nucleus-to-cytoplasm ratio. An intact Achilles tendon from a traumatically amputed limb of an older adult (TEM × 6000).

Extracellular Changes

With development and aging, both the collagen and noncollagenous matrix components of tendons show qualitative and quantitative changes. The collagen content remains unchanged or decreases slightly to 75%, while the amount of proteoglycans and glycoproteins declines more intensely. The elastic components increase into early adulthood to decrease into old age. The extracellular water content of a tendon declines from about 80% to 85% at birth to approximately 30% to 70% in old age [11,15,17]. The decrease in water and mucopolysaccharide contributes to the age-dependent changes of stiffness of tendons and a reduction in their gliding properties [1,12].

Collagen

Within the tendon, the most remarkable age-dependent changes are those that involve collagen (see Figure 4-2).

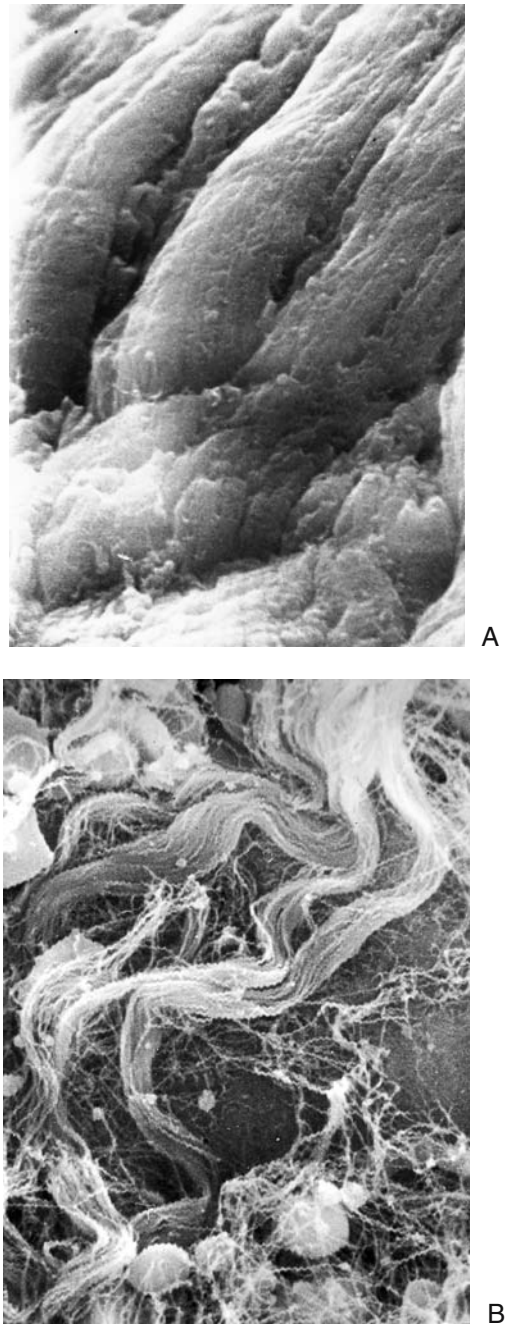

FIGURE 4-2. (A) Normal collagen bundles of an Achilles tendon of a young adult cadaver (Scanning electron microscope, SEM × 1700). (B) Disintegrated and frayed collagen bundles of an Achilles tendon of an older adult cadaver (scanning electron microscope, SEM × 1300).

With age, the absolute collagen content changes little, while the relative amount of collagen and the collagen volume density of the tendon increase due to decrease in the proteoglycan-water content. The type II collagen-containing region spreads significantly from the attachment zone of the tendon into the tendon substance [1,12,18,19]. The mean collagen fibril diameter shows a marked increase during development, while a decrease in the proportion of thick fibrils and in the mean area of the fibrils occurs with senescence [13]. Collagen turnover, which is relatively low to begin with, declines with age as collagen synthesis diminish [11,18]. Due to the age-dependent reduction of tendon cells and enzymes that are essential for collagen synthesis, repair of the soft tissues, such as tendon, is delayed in old age.

During senescence, the mechanical properties of collagen decrease [20]. This is due to changes in collagen crosslinking profile, as there is an increase in the crosslinking of the tropocollagen molecules decreasing the solubility of collagen [9,10]. The conversion to nonreducible crosslinks is a spontaneous age-related process, although mechanical stress and hormones may have an additional effect [1,21]. The increase in crosslinks has been observed to have an effect on several laboratory-detected phenomena: an increased resistance to degradative enzymes [22]; reduced solubility of collagen [2,19,23]; increased stability to thermal denaturation [2,23]; and increased mechanical stiffness [23,24]. The crosslinking of collagen is considered one of the best biomarkers of aging [25].

Elastin and Contractile Proteins

With increasing age, a decrease in the number of elastic fibers as well as many morphological changes have been observed [11,12,18]. These could be related to an increase in the synthesis of fibrillar glycoproteins associated with partial degeneration of elastin by tissue elastases [21].

The presence of the contractile proteins actin and myosin has been demonstrated in tendon cells, and these remained unchanged with age [12,17]. Anderson [26], however, found an increased actin content in old chick fibroblasts.

Other Noncollagenous Matrix Components

The extracellular water content and mucopolysaccharide content decrease with aging [2,9,12,19]. Total glycosaminoglycan and glycosaminoglycan fractions show a pronounced decrease during the maturation period. This trend continues, albeit to a lesser degree, during the rest of the life span [1]. Also, the composition of the glycosaminoglycans changes during aging, as the amount of dermatan sulfate (major component of glycosaminoglycans in tendons of newborns) decreases and chondroitin sulfate becomes prominent [27].

Blood Vessels

Tendon blood flow and the number of capillaries per unit of surface area decrease with increasing age [11]. The decreased arterial blood flow and thus decreased nutrition and oxygen transport have been suggested to be the main etiological factors behind the age-related tendon degeneration [28,29]. There are also numerous age-related pathological changes in the blood vessels of the tendon and its paratenon. (See section on age-related pathological changes below.)

Biomechanical Changes

The most drastic biomechanical change of tendon aging is decreased tensile strength [30]. The increase in collagen crosslinking widely alters the mechanical properties of the tendon as there can be found a decrease in ultimate strain, ultimate load, modulus of elasticity, and tensile strength, and an increase in mechanical stiffness [9,23,31]. The increased rigidity of collagen fibers results in a decrease in the tensile strength of a tendon [9]. It appears that there is an ideal amount of stabilized crosslinks beyond which more crosslinking stabilization becomes a maladaptive adjustment [9,23]. Other biomechanical tendon variables altered by aging are those associated with tissue viscosity, namely stress relaxation, mechanical recovery, and creep [31].

With age, the relative collagen content of a tendon increases, but the elastin and proteoglycan matrix decrease, suggesting less elasticity [11]. However, the pattern of change of the modulus of elasticity of tendon follows that of total collagen content and not of elastin [1].

Altogether, the above-noted changes make the tendon weaker than its younger counterpart and more likely to tear or suffer from overuse injury when subjected to increasing stress and strain [1].

Age-Related Pathological Changes

The most characteristic age-related microscopic and biochemical pathological changes are degeneration of the tenocytes and collagen fibers, and accumulation of lipids, ground substance (glycosaminoglycans), and calcium deposits [18]. These may occur separately or in combination, and very often these changes occur with changes in the blood vessels of the tendon or its paratenon. The vascular changes include narrowing of the lumina of the arteries and arterioles, usually due to hypertrophy of the intima and media of the vessel walls. Sometimes they are associated with deposition of fibrin, formation of thrombus, and evidence of proliferative arteritis, arteriolitis, and periarteritis [11] (see Figure 4-3). The decreased arterial blood flow and thus decreased nutrition and oxygen transport have been suggested as the main etiological and

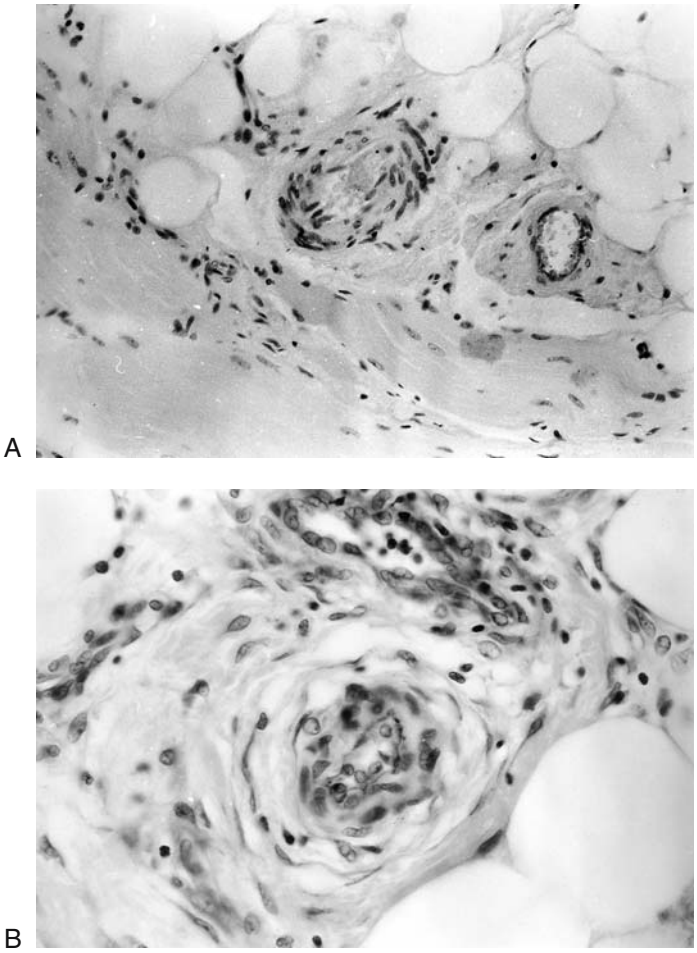

FIGURE 4-3. (A) Obliterative arteriopathy of a ruptured Achilles tendon. The vessel walls are thickened and the lumina narrowed (Hematoxylin-eosin, HE × 150). (B) Proliferative arteritis (middle) and phlebitis (above) of a ruptured Achilles tendon. The vessel walls are thickened and the arterial lumen almost obliterated (Hematoxylin-eosin, HE × 150).

pathogenetic factors behind age-related tendon degeneration [28,29], but direct evidence is still lacking.

Focal lipid deposits can be seen already at the age of 15 [32], but the process does not accelerate until the fourth decade of life [18]. The Achilles, biceps brachii, anterior tibial, and especially the quadriceps and patellar tendons are the most severely affected anatomic sites [32,33].

The most frequent form of lipid accumulation during aging is extracellular accumulation in which lipids with a high content of esterified cholesterol are spread along the axis of collagen fibers. These fine droplets are plasma low-density lipoprotein filtrates [11]. The effect of lipid deposition is to disrupt the fiber bundles and thus diminish tendon strength.

Areas of reduced blood flow and maximal lipid deposition correlate with the classical sites of tendon rupture, particularly those of the Achilles and posterior tibial tendons [28,34]. Tendon rupture is usually preceded by histopathological degenerative changes, including hypoxic degenerative tendinopathy, mucoid degeneration (Figure 4-4), tendolipomatosis (Figure 4-5), and calcifying tendinopathy, either alone or in combination, and

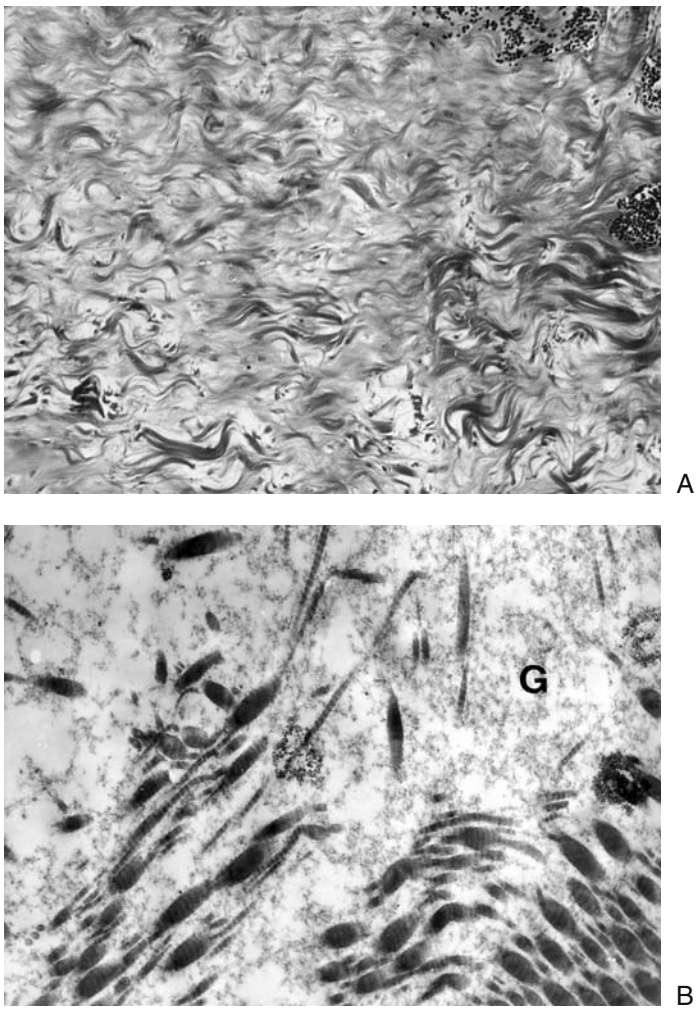

FIGURE 4-4. (A) Mucoid degeneration of a ruptured Achilles tendon. The collagen fiber structure is loose and disintegrated (Masson trichrome staining × 150). (B) Mucoid degeneration of a ruptured Achilles tendon. The collagen fibrils vary in diameter and run in various directions. Among the fibrils, large amounts of mucus-like fine granular material (glycosaminoglycans, G) is visible (TEM × 8300).

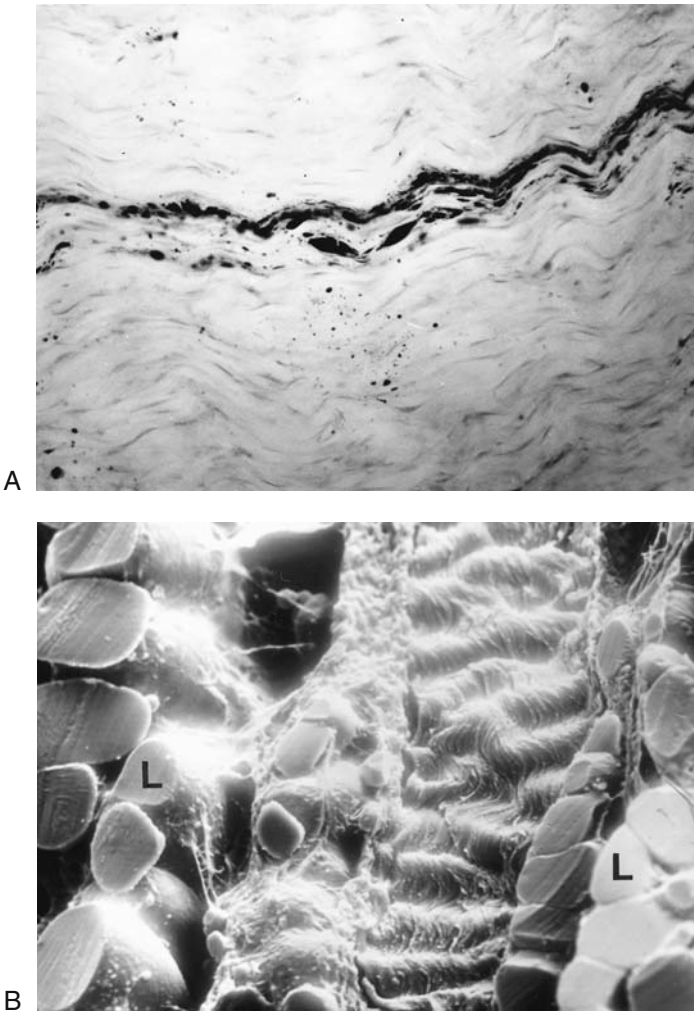

FIGURE 4-5. (A) Tendolipomatosis of a ruptured Quadriceps tendon. Lipid cells (black) have accumulated between the collagen fibers forming long chains (Sudan Black staining × 100). (B) Tendolipomatosis of a ruptured Quadriceps tendon. Lipid cells (L) have accumulated between the collagen fibers (SEM × 870).

the incidence of these degenerative changes tends to increase with age [18,35]. In patients with Achilles tendon rupture, aging has been shown to be associated with many complications after surgical and nonsurgical treatment [35]. In shoulders, in turn, rotator cuff lesions, detected by ultrasonography, are suggested as a natural correlate of aging, with a statistically significant linear increase in asymptomatic partial- or full-thickness tears after the fifth decade [36].

In clinical practice, the most disconcerting and irritating problem of tendinopathies is pain rather than the age-related pathological changes of tendon. Traditionally, the pain associated with chronic tendinopathy has been assumed to arise through one of two mechanisms: inflammation or separation of collagen fibers [37,38]. However, neither of these classical hypotheses holds up under scientific scrutiny [37–39]. As an alternative explanation for the origin of pain in chronic tendon disorders, it has been recently presented that as yet unidentified biochemical noxious compounds could irritate the pain receptors in the diseased tendon tissue [37,38]. Candidates include matrix substances, such as chondroitin sulfate or nociceptive neurotransmitters, such as substance P. However, before any extended conclusions, much future research is needed to clarify the possible cause-and-effect relationships between these candidate substances and the tendon pain.

Factors Influencing the Rate of Aging and Prevention of Age-Related Tendon Degeneration

The rate of aging is highly individual and can be influenced by many factors, including genetics, lifestyle, hormonal changes, and disease processes [9]. Thyroxine is necessary for normal development: hypothyroidism causes an accumulation of glycosaminoglycans in the connective tissue throughout the body [1]. Corticosteroids are catabolic and, especially at moderate to high pharmacological levels, they inhibit the production of new collagen. Insulin, estrogen, and testosterone increase the production of collagen to varying degrees by preventing excessive collagen breakdown [10]. Hamlin et al. [40], for example, showed that collagen from 40-year-old diabetics corresponds to that of normal individuals at 100 years of age. Nutritional deficiencies can also be associated with tendon degeneration. Adequate food supply of proteins is needed for the necessary amino acids of collagen and other proteins, and of carbohydrates for the maintenance of the ground substance.

Tendons are altered structurally and chemically by activity, and even more so by inactivity. Exercise appears to have a beneficial effect on aging tendons [11,41]. Long-term exercise increases the mass, collagen content, cross-sectional area, ultimate tensile strength, weight-to-length ratio, and load-to-failure of tendon tissue [11,24,42–44]. Although these positive effects of exercise on tendon properties are relatively small, the rate of degeneration with age can probably be reduced by regular activity. Sedentary lifestyle, in turn, is probably one of the main reasons for poor circulation in tendons [18]. On the other hand, some elderly athletes suffer from overuse-related and degenerative sports injuries, including tendinopathies.

In clinical practice, to prevent age-related tendon degeneration and related symptoms, maintenance of flexibility and neuromuscular coordination through daily stretching and calisthenics is recommended. Long warm-

up and cooling-down periods should be the rule. The advice about slow increase in the intensity, duration, and frequency of training is especially suitable for elderly people. Finally, special attention and caution should be paid to sports in which the lower extremities are fully weight-bearing with strong impacts and quick acceleration and deceleration movements, such as running and fast ball games with repeated jumping. Thus, particularly in elderly athletes, participation in sports like swimming, cycling, and walking, in which the whole body weight is not on the lower extremities or the impact effects and muscle forces are lower, is recommended.

Summary

The changes associated with increasing age result in a decline in the structure and function of human tendons. Age correlates with decrease in the number of tenoblasts and overall tenoblastic activity. Structurally, collagen fibers increase in diameter, vary in thickness, lose tensile strength, and become tougher with increasing age and so the ultimate tensile strength of a human tendon declines.

Age also affects tendon blood flow and the number of capillaries per unit of surface area. The most characteristic age-related microscopic and biochemical pathological changes are degeneration of the tenocytes and collagen fibers, and accumulation of lipids, ground substance (glycosaminoglycans), and calcium deposits.

Careful control and treatment of nutritional deficits and altered hormone levels, whether due to disease or pharmacological intervention, may reduce the harmful aging effects on tendon tissue. Also, participation in a well-structured, long-term exercise program may minimize or retard the effects of aging on tendons.

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5
Epidemiology of Tendon Problems in Sport

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Introduction

The role of sport and physical activity has become more important in all modern countries in the last four decades. Competitive and professional sports have received much attention in the media, thus increasing the demands on sports performances. This has been followed by the increased risk of sports injuries, especially overuse injuries, as athletes are required to train more intensely and for longer. Previously, sports and physical activities interested mainly young and, at most, middle-aged men and women. However, the trend today, with increase in leisure time, shorter working hours, and lighter physical labor, has led to a greater number of individuals in all age groups spending more time practicing sports, both competitive and recreational [1,2]. In Finland, a population of 5 million experiences more than 200 000 acute sports-related injuries yearly, a greater number than the number of traffic injuries [1]. The number of overuse injuries is not known exactly, but in the United States it is estimated to be about 30% to 50% of all sports-related injuries [3].

The exact incidence of any type of overuse injury is even more difficult to establish, since the injury definition is ambiguous, diagnosis sometimes difficult, and the population at risk often unknown [4–7]. In addition, these injuries are often treated in different settings, such as sports injury clinics, hospitals, primary care units, physical therapy departments, and private clinics, and by many types of specialists, such as specialized and nonspecialized sports physicians, pediatricians, chiropractors, naturopaths, physical therapists, and athletic trainers. The only certainty is that the absolute number of overuse injuries has increased dramatically during the last few decades due to general increase in sporting activities [8–11]. Claims about the relative increase, or increase in the incidence of overuse injuries, still lack scientific evidence.

Physicians in primary care, sports medicine, and orthopedics see patients with overuse tendon conditions nearly every day. These overuse tendon problems are not restricted to competitive athletes, but affect recreational sports participants and many working people. The pathology underlying these conditions is tendinosis or collagen degeneration [12].

Tendon injuries are typical of, and a common occurrence in, sports, because during physical activity much stress and force are focused to the tendinous part of the muscle-tendon unit, increasing the risk of tendon injury. Athletes who exercise daily often suffer from overuse injuries, over half of which involve tendons, tendon sheaths, and tendon insertions [10,13,14]. Komi et al. [15] showed that, in many activities such as running, jumping, and hopping, the peak Achilles tendon force exceeds 9 kN, corresponding to about 12.5 times body weight. However, the ground reaction forces measured during these activities are much lower, indicating that, in addition to force transmission from muscle to bone, the tendon plays an important role as an active element of the muscle-tendon unit by storing elastic energy during strenuous sporting activity [8,16].

Running is one of the most popular leisure sports activities and is integral to the training of almost every sport. The overall yearly incidence rate for running injuries varies between 24% and 65% [6,7,17]. About 50% to 75% of all running injuries are overuse injuries due to constant repetition of the same movement, with most injuries occurring in the tendons around the knee or in the Achilles tendon [13].

Epidemiology in Sports Medicine

The aims of epidemiologic research are 1) to describe the health status of populations by quantifying the occurrence and time trends of diseases; 2) to obtain the relative frequencies and definite health trends within groups; 3) to explain the origin of diseases by determining the factors that cause specific diseases or trends; 4) to predict the number of disease occurrences and the distribution

of health status within populations; and 5) to control the distributions of diseases in the population by the prevention of new occurrences, eradication of existing cases, prolongation of life with disease, or improvement of the health status of afflicted persons [18].

In epidemiology, two basic terms are distinguished: incidence and prevalence. Incidence of injuries is defined as the number of new occurrences in a population during the period of observation. Prevalence of injuries pertains to the total number of cases of a disease or condition at a specified point or period. In sports medicine, however, as in all clinical medicine, the data presented are often incompletely gathered in a nonrandom retrospective or prospective manner and without either control populations or prior formulation of study questions. Therefore, there are often difficulties in obtaining answers to specific questions [8,18].

In sports medicine, epidemiological studies are important when planning prevention programs for sports injuries. The sports cultures of individual nations and different sports habits in different countries also mean that national epidemiologic studies are necessary in each individual country [19].

In many European countries, about 50% of all sports injuries are caused by soccer [20]. However, in Finland, for example, overuse sports injuries are common owing to the widespread popularity of endurance sports, especially running and jogging [10,21,22].

Many epidemiological reports from sports clinics have been published without indicating the true incidence or prevalence of sports injuries. They do, however, indicate which are the main problems in practical sports medicine and serve as a good basis for studying the different factors in the background of these injuries. This chapter discusses the occurrence of both overuse and tendon injuries in sports and the etiological factors, intrinsic and extrinsic, of these injuries. The main intrinsic and extrinsic factors relating to tendon injuries are illustrated in Table 5-1 [11].

Table 5-1. Factors associated with overuse tendon injuries

Intrinsic
Malalignments: excessive ankle pronation, genu valgum/varum, femoral neck anteversion, other
Limb length discrepancy
Muscular imbalance
Muscular weakness
Hypermobility of joints
Lack of elasticity (inflexibility)
Extrinsic
Training errors: distance, intensity, hill work, technique, and fatigue
Surfaces
Environmental malconditions
Footwear and equipment

Table 5-2. Common sites of tendon injuries

Tendon involved	Name of injury
Achilles tendon	Achilles tendinopathy, Achilles peritendinitis, Achilles tendinosis, Achilles insertiotendinopathy, tendon rupture, calcaneal apophysitis (Sever's disease)
Patellar tendon	Patellar tendinopathy, patellar peritendinitis, patellar tendinosis, patellar apicitis (jumper's knee), apophysitis at the tibial tuberosity (Osgood-Schlatter disease)
Tractus iliotibialis	Iliotibial tract friction syndrome
Biceps femoris, semitendinosus, semimembranosus, proximal parts	Hamstring syndrome
Rotator cuff tendons	Subacromial pain syndrome, traction overload tendinopathy, impingement syndrome, swimmer's shoulder, rotator cuff tendinosis, and/or tear
Common wrist extensors, proximal insertion	Lateral epicondylalgia (tennis elbow)
Common wrist flexors, proximal insertion	Medial epicondylalgia (thrower's elbow, golfer's elbow)

The most common tendon injuries in sports are presented in Table 5-2. The anatomic sites of sports-induced overuse injuries of tendons are usually more common in the lower than in the upper extremities. The opposite is true in work-related overuse problems [6–9]. The Achilles and patellar tendons are the most commonly affected anatomical sites, although there is a large variation among different sports. It is characteristic of sports-related tendon problems that, depending on the varying nature and often very specific demands of different sports events, tendon injuries can be in any of the extremities, while work-related overuse injuries are more concentrated in certain tendons and tendon insertions in the upper extremities.

The intrinsic and extrinsic factors have varying significance in the background of different tendon problems in sports, but some factors (age and gender) concern most tendon disorders and need, therefore, a more detailed discussion.

Age

In adolescents, apophysitis and insertional tendinopathy are more frequent than problems in the midsubstance of the tendon [8]. In growing athletes, Osgood-Schlatter disease is the most common tendon complaint, representing more than 10% of all sports-related overuse injuries [9,23,24]. Calcaneal apophysitis (Sever's disease) is another common overuse injury in adolescents, repre-

senting 6% to 15% of all overuse problems in this age group [23,24]. In master athletes, overuse problems are more common than acute injuries, most likely because most of them are involved in endurance sports. In a 3-year prospective study in a Finnish sports clinic, shoulder complaints (18%, usually affecting the rotator cuff) and problems of the Achilles tendon and of the other calf tendons (20%) were more common in this age group than in 21- to 25-year-old athletes [25].

Gender

The majority of overuse tendon injuries occur in men, although the incidence in women seems to be increasing. The male-to-female ratio in total Achilles tendon ruptures varies between 7 to 1 and 4 to 1 in different studies [26–29]. Although 60% or more of all overuse injuries sustained in running are found in men, women under the age of 30 are considered to be at the greatest risk for these injuries. The proportion of female participants in sports injury surveys has increased during the past few decades, from 14% to 18% to 20% to 30% [13,22,30–32]. This could result from the increased interest of women in sports and physical activity in general. Second, women are now much more interested in sports that have a high risk not only of acute injury (football, downhill skiing, judo, and indoor ball games), but also of overuse injury (long-distance running, aerobics, cycling, triathlon, and indoor ball games) [8,31].

Epidemiology of Tendon Injuries

Achilles Tendon Overuse Injuries

The occurrence of Achilles tendon overuse injuries is highest in middle- and long-distance running, orienteering, track and field, tennis, and other ball games [32–34]. Johansson [35] and Lysholm and Wiklander [36] reported an annual incidence of Achilles tendon overuse injuries in top-level runners of 7% to 9%. The most common clinical diagnosis of Achilles overuse injuries is tendinopathy of the main body of the tendon (55% to 65%), followed by insertional problems, such as retrocalcaneal bursitis and insertional tendinopathy (20% to 25%).

The etiology of Achilles tendon overuse injuries is multifactorial [37]. Training errors have been reported in 60% to 70% of the running injuries [36,38]. The most common training errors associated with Achilles tendinopathy, as for many other overuse injuries, are a rapid increase in mileage, increased intensity of training, and running on sloping and slippery roads [38,39].

Kvist [13,33] studied the epidemiological factors associated with Achilles tendon injuries in a large group of sports patients. Of the 698 cases included in those studies, 66% had tendinopathy and 23% Achilles tendon insertional problems. In 8% of the patients, the injury was located at the myotendinous junction, and 3% of all patients had a complete tear of the tendon. Of the patients with an Achilles tendon injury, 89% were men. Running was the main sports event in patients with an Achilles tendon injury (53%), while running sports patients represented 27% of all patients studied in this clinic. Some malalignments of the lower extremity were found in 60% of patients with Achilles tendon overuse injury.

A varus of the forefoot correlated significantly with Achilles tendinopathy [13,37]. Also, limited subtalar joint mobility and rigidity of the ankle joint were more frequent in athletes with Achilles tendinopathy and insertional complaints than in other athletes [13]. This contrasts with the report by Segesser at al. [40], who found ankle joint instability and hyperpronation to predispose to Achilles tendon disorders. In general, different malalignments and biomechanical faults are claimed to play an etiologic role in 60% to 70% of the athletes with Achilles tendon overuse injuries [33]. These injuries occur at a higher rate in older athletes than do most other typical overuse injuries. In a report on 470 patients with Achilles tendinopathy and insertional complaints, about 25% of the subjects were young athletes, with 10% younger than 14 years, and there was a significant connection with calcaneal apophysitis (Sever's disease) in this latter age group [13].

Although almost all known intrinsic and extrinsic predisposing factors to Achilles tendon overuse injuries are commonly seen bilaterally, the symptoms of Achilles tendon overuse injuries are usually initially unilateral. However, Paavola et al. [41] showed, in their observational 8-year follow-up study, that in the long run patients with unilateral Achilles tendinopathy seem to have a relatively high risk to get the symptoms of overuse (exertional pain with or without swelling and stiffness) to the initially uninvolved Achilles tendon, too. In that study, in 34 of the 83 patients (41%), the overuse symptoms developed also to the contralateral side.

Achilles Tendon Rupture

Achilles tendon ruptures were apparently rare before the 1950s, but the incidence has recently increased in developed countries [28,42]. A bimodal age distribution (peak in the fourth decade of life followed by a second, but lower, peak in the sixth to eighth decade of life) among patients with a rupture has been noted in most of the studies [43–46], and this probably represents two different etiologies of Achilles tendon rupture. Especially in the younger age group, the majority of Achilles tendon ruptures are related to sports that require sudden acceleration and jumping [28,43,47]. In the study of

Schönbauer [47], 755 of nearly 4000 ruptures of the Achilles tendon were related to sports activities. The incidence of Achilles tendon ruptures in men is about 1.7 to 7 times greater than in women [26–28,46]. The first peak in incidence of Achilles tendon rupture is between 30 and 40 years of age, lower than the age in patients with other spontaneous tendon ruptures [28]. In some studies [43,45], the second peak has been found between 50 and 60 years, and in some other studies [44,46] between 70 and 80 years, closer to the mean age of patients with other types of tendon ruptures.

The distribution of Achilles tendon ruptures by different sports varies considerably from country to country, according to the national sports traditions. For example, in northern and middle Europe, soccer, tennis, track and field, indoor ball games, and downhill skiing, and in North America, football, basketball, baseball, tennis, and downhill skiing dominate the statistics (see Table 5-3). However, during the last decade, Leppilahti at al. [43] and Möller et al. [44] reported that ball games covered about 90% of all sports-related Achilles ruptures, and both reported that badminton-induced ruptures showed a sharply increasing incidence, with this sport now being the number one sport in causing Achilles ruptures in Sweden and Finland. On the other hand, in some countries downhill skiing has been reported to be the most common cause of Achilles tendon rupture [27].

Although people's general lifestyle has become more sedentary and physically less demanding during recent decades, increasing leisure time, and especially increased recreational and competitive sports activity, has resulted in a greater incidence of acute and overuse sports injuries [16,19,30,48]. In the pathogenesis of tendon ruptures, the more sedentary lifestyle may have resulted in decreased blood flow and nutrition of tendons and subsequent tendon tissue degeneration. This, combined with casual strenuous physical activity that heavily loads the tendon, may lead to tendon rupture [16]. When studied histologically, degenerative changes were found in nearly all Achilles tendon ruptures [49,50].

Patients suffering from partial rupture of the Achilles tendon are frequently (50% to 90%) active in sports and younger than the patients who sustain total rupture [51]. In neglected cases, granulation tissue and fibrotic scar may be formed at and around the rupture site, followed by persistent pain and disability during sports activities [52].

Table 5-3. Distribution of ruptures of the Achilles tendon according to sports

Sport	No. of ruptures	%
Soccer	458	24
Badminton	196	10
Handball	163	9
Gymnastics	161	9
Skiing	151	8
Track/running	134	7
Tennis	129	7
Jumping	93	5
Basketball	88	5
Volleyball	64	3
Cycling	43	2
American football	41	2
Squash	29	2
Others	129	7
Total	1879	100

Data from the following four studies: Jozsa et al. 1989, Leppilahti et al. 1996, Nillius et al. 1976, and Willis et al. 1986.

Patellar Tendon Overuse Injuries

About one-third of sports injuries that are treated at outpatient sports clinics involve the knees [22,53–55]. The most common knee disorders are Osgood-Schlatter disease and patellar tendinopathy. Of the 2800 athletes in the Turku Outpatient Sports Clinic, about 700 male and 190 female patients had suffered a knee disorder [54]. The highest incidences were in soccer (21%), long-distance running (13%), volleyball (12%), orienteering (8%), and ice hockey (7%). The most common knee disorders were insertional tendinopathy at the lower pole of the patella (at the proximal end of the patellar tendon), or jumper's knee (20%), Osgood-Schlatter disease (10%), and patellar tendinopathy (6%). Martens et al. [56] found that volleyball and soccer were the sports in which two-thirds of all their patients with patellar tendinopathy were involved. Blazina et al. [57] found that patients suffering from jumper's knee were usually tall athletes, but Martens et al. [56] did not confirm this association.

Overuse injuries of the patellar tendon are most common in athletes involved in some type of repetitive activity, such as jumping (volleyball, basketball, high jump, and triple jump), kicking (soccer, football), quick stops and starts (tennis, squash, badminton), running (sprinters, endurance runners), weightlifting and power lifting, and bicycling [56–62]. Frequently, tenderness and tissue pathology are localized at the patellar tendon origin at the inferior pole of the patella.

Kujala et al. [21,63] have studied the role of different anatomic factors relative to jumper's knee and patellar tendinopathy, and they found a significant correlation between leg length inequality and patella alta and patellar tendinopathy. Increased laxity of the knee joint correlated, in its turn, with patellofemoral pain syndrome. In patellar tendinopathy, the pathologic changes are most often located at the insertional areas, where micro- or macroruptures and tissue degeneration are often found [59]. In volleyball, landing from a jump (eccentric loading) and repeated direct striking of the knees on the floor may play a role in the etiology of the patellar

tendinopathy [64]. Cook et al. [65] studied athletes with jumper's knee, and found that in 48% of patients the symptoms began before the age of 20 years. The predominance of males was noted, a finding evident also in other prospective studies [59,66].

In a prospective study of Kannus et al. [9], Osgood-Schlatter disease (or traction apophysitis of the tibial tuberosity) was the most common athletic overuse injury in boys (18% of all injuries) and the second most common in girls (13%). Similar data have been found in a retrospective study of 185 consecutive osteochondroses [67]: Osgood-Schlatter disease was the most frequent osteochondrosis (30%), followed by Sever's disease (23%). In a study of Kujala et al. [23], Osgood-Schlatter disease was the most frequently seen complaint in sports-active adolescents at the age of 13 years (peak).

Iliotibial Tract Friction Syndrome

An exertional pain, associated commonly with hard running and felt on the lateral femoral condyle, has been named as iliotibial tract friction syndrome, or "runner's knee" [68]. This complaint represented about 2% of all knee problems in the Turku Outpatient Sports Clinic [54], but it was three times as common in other areas of the same country [10]. Newell and Bramwell believe that approximately 14% of patients with overuse injuries of the knee had iliotibial tract friction syndrome [55].

The majority of patients with iliotibial tract friction syndrome are runners. In Orava's report [69] of 88 patients, 55% were long-distance runners or joggers, and 15% were skiers. Downhill skiers, soccer players, circuit trainers, weightlifters, cyclists, and athletes who participate in jumping sports may also suffer from the syndrome [68–75]. The iliotibial tract friction syndrome was found to be the sixth most common overuse syndrome in runners [76].

Hamstring Syndrome

The condition in which pain is felt over the area of the ischial tuberosity and radiating down the back of the thigh has been named hamstring syndrome [77]. Normally, the sciatic nerve passes lateral to the biceps femoris muscle near the ischial tuberosity and then under the thigh muscles. The hamstring muscles have a thick, tendinous structure near their site of origin. In the hamstring syndrome, this fibrous region is distinct and tense like a violin string. In some cases, there are adhesions between the sciatic nerve and the tendon [77].

The pain in hamstring syndrome characteristically occurs when sitting, for example, while driving a car or sitting during lectures. It is typically induced by forcibly driving the leg forward, as in sprinting or hurdling. Hamstring stretching also causes the pain at the tuberosity, as does kicking a ball. A great majority of the athletic patients with hamstring syndrome are active in sprinting, hurdling or jumping (50%), and soccer (22%) [77].

Rotator Cuff Problems

Anterior shoulder pain caused by soft tissue (muscles, tendons, ligaments, and bursae) dysfunction of the shoulder girdle is the most common shoulder problem in people aged 15 to 60 years of age. The group of specific diagnoses responsible for anterior shoulder pain should be classified as "subacromial pain syndrome" rather than "impingement syndrome" [78]. Although true impingement syndrome is probably the most common source of pain within subacromial pain syndrome, traction overload tendinopathy, true calcifying tendinitis, shoulder instability with secondary impingement, and partial- and full-thickness cuff tears as a chronic manifestation are all part of the subacromial pain syndrome [16].

Impingement syndrome is a symptom complex characterized by anterior shoulder pain exacerbated by activities at the shoulder level or above. Sports requiring repetitive overhead motions may cause injury to the cuff by compression, as in throwers and racquet sports players [79]. Alterations in the bony anatomy of the acromion may also reduce the available space for the rotator cuff tendons, and thus predispose to impingement. The patients are usually over 40 years of age and reveal pathologic changes of varying degrees in the components of the subacromial space.

Traction overload tendinopathy has a similar presentation to that of primary impingement syndrome, although it occurs usually in younger (under 35 years of age), more active age groups [78]. Although similar symptoms may exist between these conditions, a predominant feature of traction overload tendinopathy is pain, mainly with physical activities. Sports requiring repetitive use of the arm at or above the horizontal and high strains within the tendon during the declaration phase, such as the tennis serve, the volleyball hit, and javelin and ball throwing, may produce overloading, inflammation, and degeneration in the rotator cuff tendons [16,78,79].

Rotator cuff ruptures are rare in persons under 30 years of age, with most patients over age 50 [16]. Men are more often affected than women, with the male-female ratio varying from 4:1 to 10:1. Complete rotator cuff tears are rare in young athletes, who more frequently suffer from impingement problems, partial tears, or both. Sports with high-force throwing movements, such as American and Finnish baseball, javelin and discus throwing, and football characteristically produce these injuries [79]. Tibone et al. [80] analyzed 55 athletes who were operated upon for a partial or complete rotator cuff tear. The primary sport involved was baseball for 29 shoulders (20 pitchers and 9 fielders), tennis for 4, volleyball for 2,

and miscellaneous for 6. In most cases, the rotator cuff tear was thought to be due to chronic overuse of the shoulder in repetitive overhead activity.

Lateral and Medial Epicondylopathy

Lateral epicondylopathy (classic tennis elbow), also previously known as lateral epicondylitis, is perhaps the most common insertional tendinopathy of the human body. The cause of lateral epicondylopathy is excessive, monotonous use of the wrist extensors and forearm supinators [8,81]. Its incidence varied from 31% to 41% in 5 reports consisting altogether of 3676 tennis players [82]. Gruchow and Pelletier [83] reported that the incidence of tennis elbow was 2 to 3.5 times higher in the over-40 age group than in those under 40, and among those respondents who played more than 2 hours a day than among those who played less than 2 hours a day.

Medial epicondylopathy of the humerus, or "golfer's elbow," "thrower's and pitcher's elbow," or "medial tennis elbow" is a less common clinical problem than lateral epicondylopathy. Medial epicondylopathy in tennis is 7 to 10 times less common than lateral epicondylopathy [82]. Medial epicondylopathy is characteristic of golfers, throwers, and pitchers; the deceleration phase of the throwing movement is probably responsible for the repetitive overload that initiates the development of the condition [16].

Summary

During the last few decades, the role of sports and physical activity has become more and more important in all modern communities. Sports activities are generally considered beneficial by many governments because of their effect on well-being. The risk of injury is increased, for both acute traumas and overuse injuries, and prevention has also become an integral part of sports medicine. Epidemiological studies are important when planning prevention programs for sports injuries. Because of individual sports cultures and different sports habits in different countries, national epidemiological studies are needed in each individual country.

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6
Neurogenic, Mast Cell, and Gender Variables in Tendon Biology: Potential Role in Chronic Tendinopathy

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Introduction

Tendinopathies are frequent complications of athletic activities and of certain occupations, and occur as secondary sequelae of some diseases. The incidence, and awareness, of repetitive motion syndromes and overuse syndromes affecting tendons has increased in recent years. These increases may be in part be related to increased participation in recreational sports, increased numbers of individuals involved in some occupations, and/or increased reporting of such complaints. While some problems, particularly occupation-related cases, can likely be traced to ergonomic considerations, a number of other factors such as genetics, gender, and fitness levels could also play a role in either the initiation of such tendinopathies or their progression to loss of function. In athletes, a number of other factors may also contribute to tendinopathy development [1]. However, most of these cases respond to conservative treatment [2,3].

A review of this field was published in 1995 [4], and the reader is referred to that information source, or other chapters in this monograph, for many aspects of the problem which will not be rediscussed in this chapter. Since 1995, the problem of the prevention, diagnosis and effective treatment of tendinopathies have evolved somewhat, but much is still unknown regarding the inciting events and the mechanisms responsible for the progression of the problems. Because not all individuals involved in a particular athletic activity or occupation develop tendinopathies, it is difficult to identify factors that could contribute to either initiation or progression of these tendon problems. Similarly, not all patients respond to existing treatments equally. Some respond to rest and anti-inflammatory interventions, while others are either nonresponsive or relapse as soon as activity levels are reinstituted. Thus, there is a need for more basic information on the regulation of tendons at the level of cell and molecular biology, as well as physiology.

Tendons are not all the same, a fact that complicates understanding of disease development and progression. While they all have intrinsic cells (tenocytes), have a vascular supply, and are innervated, they appear to be differentiated to perform functions unique to specific environments. Some tendons have a surface layer of cells that may be unique (epitenon), while others are surrounded by a paratenon, and still others function in a sheath lubricated by synovial fluid. In addition, some tendons are differentiated along their length and may contain fibrocartilage-like areas where they traverse bony prominences [6]. Thus, tendons are complex structures that connect muscles to bones, and an understanding of the workings of one tendon likely cannot be extrapolated to tendons in other environments.

The study of tendinopathies, particularly those of the upper extremities, has been hampered by a number of limitations. One of the major limitations is at the level of understanding the etiology of tendinopathy. Most patients present with established disease, which is treated conservatively. If the condition persists, more invasive options can be entertained, but this means that clinical samples are potentially available for assessment only from individuals with advanced tendinopathy. Thus, the critical window of early disease is usually not available for study.

The second major limitation to our understanding of the regulation of tendons at the cell and molecular biology, biochemical, and physiological levels is the paucity of animal models which "mimic" human tendinopathies, particularly those involving the upper extremities. While it could be argued that the study of tendons in quadrupeds cannot mimic conditions in bipeds, the availability of animal models could assist in our understanding of potential regulatory mechanisms in these tissues. While there is not a "wealth" of animal models available, a number of recent reports indicate that new models are being developed and characterized and may share some characteristics with human disease [7–10].

One model that has received some investigative attention is that of Backman et al. [11,12], who studied overuse

injury development in the Achilles tendon complex of the rabbit. Subjecting rabbits to several weekly bouts of loading led to development of histological changes in the paratenon and tendon, which were consistent with what may occur in humans. The changes were dependent on the length of time the animals were chronically loaded, and the number of cycles of loading per minute the legs were subjected to during each loading experience. However, based on the weights of the rabbits used in these experiments, it is likely that the animals were skeletally immature. If this is true, then repetitive motion induced changes in a growing tendon could be different from those induced in tendons when the animals are skeletally mature. Similarly, based on the loading cycles per minute (150 cycles/min) required to observe changes in the tendons, it is likely that the loading regimen used in these studies was supraphysiologic.

Studies undertaken using a modified Backman protocol in skeletally mature (1-year-old animals) for up to 11 weeks of chronic loading (75 cycles/min, 3x per week, 2 hr per exposure) has not led to extensive changes in the paratenon or the tendon at the molecular or histologic levels, although there were some trends observed [13,14]. Therefore, there are some limitations to this model that may indicate that it has limited approximation to what is occurring in mature humans, although it cannot be ruled out that the ease in inducing disease in skeletally immature animals could be relevant to conditions arising in young elite athletes.

Recent studies from this laboratory have taken a somewhat different tack and focused on better understanding of potential regulatory systems that may influence the function of normal tendons in order to gain insights into potential points of failure, and which, in turn, could lead to tendinopathy development or areas which could contribute to disease progression. We have focused our efforts on neurogenic regulation of tendon cell function and how gender-related variables may affect this regulation. The studies are related to the hypothesis raised in a previous review, which proposed that neuroregulation of inflammation in tendons could be a contributing factor in the development and progression of at least a subset of tendinopathies [5]. This hypothesis proposed that neuropeptides, either directly or indirectly through tissue mast cells, are involved in normal tendon regulatory control, and during development of tendon dysfunction this regulatory "loop" becomes dysfunctional and contributes to either inflammation in the tissues or a failure to mount a productive repair response. This hypothesis is outlined in Figure 6-1, and laboratory investigations and literature evidence in support of the proposed regulatory schemes will be discussed throughout this chapter.

Neuropeptide Influences on Tendon Cell Activity

As mentioned above, tendons are innervated [5]. The paratenon of some tendon complexes is more highly innervated than are the corresponding tendons. Some of the innervation parallels the microvasculature of the tissue, as it does in ligaments. However, some of the

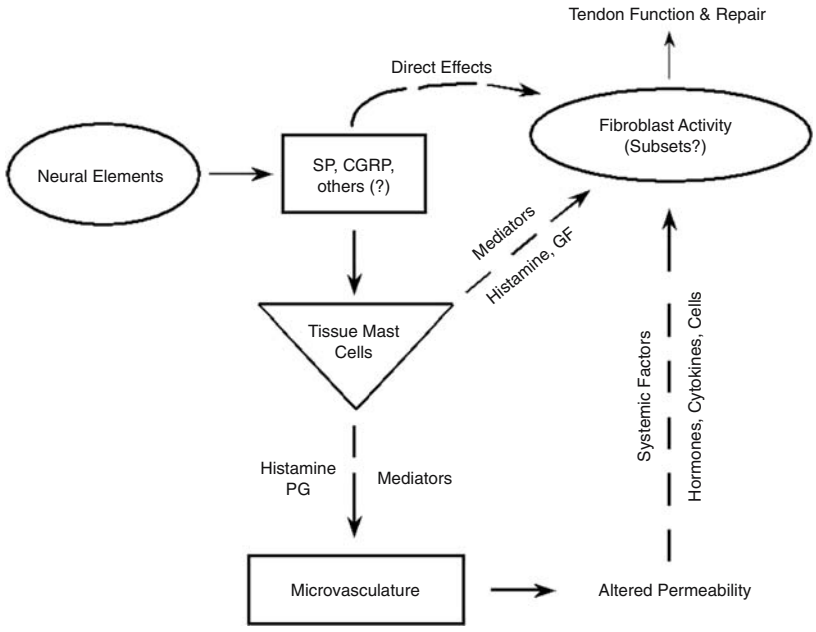

FIGURE 6-1. Model for neurogenic involvement in the regulation of tendon cells either directly or indirectly through mast cells. SP = substance P; CGRP = calcitonin gene-related peptide.

neural elements terminate in the tissues in close proximity to tissue mast cells. This proximity, and the known activity of mast cells, has raised the possibility that the neural element–mast cell interaction may lead to release of mast cell components which, in turn, could influence both the endogenous fibroblast-like cells, as well as contribute to inflammation (neuroinflammation) in the tissues through release of mediators which affect endothelial cells and vascular permeability [5]. The neuropeptides detected in tendons and ligaments are primarily substance P (SP) and calcitonin gene-related peptide (CGRP) [5], although it is likely that other neuropeptides are also present. Based on these observations, SP and CGRP were selected for testing on rabbit tendon tissue in an explant system to assess whether they could influence mRNA levels for relevant genes in these tissues.

Samples of Achilles tendon and paratenon tissue were incubated with or without optimal concentrations of SP or CGRP for 24 hours. Then mRNA was extracted from the tissues and assessed by RT-PCR [15]. When a set of 12 mRNA species were assessed (growth factors, inflammatory molecules, proteinases/inhibitors), the results indicated that a unique subset of the genes assessed were significantly influenced by exposure to the neuropeptides [16]. Interestingly, the subset of genes influenced by exposure to neuropeptides was peptide specific, gender dependent, and was altered when tissue from pregnant females was assessed. As not all of the genes assessed were altered by exposure to the neuropeptides, the responsiveness was selective and not a general response. Furthermore, the pattern of responsiveness of the paratenon was somewhat different from that of the Achilles tendon midsubstance, so there was a tissue specificity to the response as well. While the list of genes assessed was not exhaustive, the findings do support the conclusion that neuropeptides can alter cell activity in tendons. Obviously, one limitation of the experimental design is that one cannot determine whether a subset of tenocytes was responding to the neuropeptides, or whether all cells were responding equally. Additional experiments, possibly using in situ hybridization approaches, could differentiate these possibilities. Finally, it should be noted that SP and CGRG exposure did not alter expression/mRNA levels for most of the "proinflammatory" molecules assessed (IL-1, COX-2, iNOS), and therefore these neuropeptides cannot be considered overtly proinflammatory in normal tissues.

The finding of differences between males and females in the above-discussed experiments may indicate that sex hormones impact on tendon cell biology and modify neuropeptide responsiveness. We have demonstrated the presence of mRNA for the estrogen receptor (ER) and the progesterone receptor (PR) in a number of tendons from the rabbit [17]. While all of the tendons assessed (Achilles tendon, patellar tendon, extensor digitorum, and flexor digitorum longus) expressed ER and PR transcripts, the impact of pregnancy on the tendons was different in the different tendons, when assessed at the mRNA level [17]. Therefore, the pregnancy-associated effects were either due to factors other than estrogen and progesterone (i.e., the pregnancy-associated hormone relaxin), or were due to tendon-specific differences in responsiveness to estrogen/progesterone. Alternatively, as there are at least two different forms of the estrogen receptor (ER) (alpha and beta) with different activities [18,19], it may be possible that different tendons express different forms of the ER and thus respond to ligand with a pattern of responsiveness that is based on the form of ER present. Experiments to date have identified ER-alpha in tendon tissue, but we have thus far been unsuccessful in developing reagents necessary to identify ER-beta in rabbit systems. However, both ER-alpha and ER-beta are present in human ACL tissue based on RT-PCR results [Kydd, Sciore, and Hart, in preparation], so other connective tissues may also have both forms of the ER. While additional investigations are required to delineate the mechanism(s) involved, it appears that pregnancy leads to alterations in neuropeptide responsiveness in both tendons and ligaments [15,17]. Whether these alterations can contribute to gender-specific differences in tendon function and regulation remains to be elucidated. It is still controversial as to whether gender-specific factors influence development of tendinopathies [20,21].

Interestingly, inflammatory responses are attenuated in many females during pregnancy [discussed in 22], and some women with diseases such as rheumatoid arthritis experience remissions during pregnancy. Some evidence does exist for transient Achilles tendinopathy resolution during pregnancy (Maffulli et al., personal communication), and pregnancy-associated carpal tunnel syndrome has been reported [23,24]. The latter condition usually resolves in the post-partum period [23].

Influence of Hysterectomy + Ovariectomy on mRNA Levels in Tendons

If indeed there are differences between males and females in regulating responsiveness to neuropeptides in tendons, and estrogens play a role in modifying cell activity in such tendons, then one might expect that removal of estrogen producing tissues (ovaries and uterus in the rabbit) would impact gene expression levels in the tendons. To start to approach this question, mRNA levels for a subset of genes that could be involved in inflammatory responses in tendons were compared between female rabbits subjected to hysterectomy and ovariectomy prior to the onset of sexual maturity (2 months of age) and control (sham) animals. The Achilles tendon and paratenon, and the patellar tendons were removed after sacrifice at 7 months of age. As shown in Table 6-1, mRNA levels for some, but not all, genes assessed were influenced by removal of estrogen producing tissues.

While this was an initial study, the results indicate a few important points. First, the response of the patellar

Table 6-1. Influence of ovariectomy + hysterectomy on mRNA levels in rabbit tendons

	Achilles tendon		
Gene	Paratenon	Midsubstance	Patellar tendon
COX-2[a]	↑[b]	↑	—
iNOS	—	↑	↓
TNF	—	↑	↓
UK	—	—	↓
MMP-1	—	—	—
MMP-3	↑	—	—

[a] COX-2 = cyclooxygenase-2; iNOS = inducible nitric oxide synthase; TNF = tumor necrosis factor; UK = urokinase; MMP-1 = matrix metalloproteinase-1; MMP-3 = matrix metalloproteinase-3.
[b] Change relative to mRNA levels in age-matched control animals.

tendon to removal of the major estrogen producing tissues prior to sexual maturity was different from the response of the Achilles tendon components. In the patellar tendon, ovariectomy and hysterectomy led to decreased transcript levels for iNOS, TNF and the proteinase urokinase (UK), but no change in COX-2, MMP-1, or MMP-3 mRNA levels. In contrast, in the Achilles tendon ovariectomy and hysterectomy led to increases in transcript levels for COX-2, iNOS, and TNF, but not UK, MMP-1, or MMP-3. The response of the paratenon of the Achilles tendon was less evident, with all but COX-2 and MMP-3 unchanged. The second point is that mRNA levels for all of the assessed genes were not altered by removal of the major estrogen producing organs. Therefore, there was specificity to the changes. A third point, which is more speculative, is that one might expect that it may be easier to induce an inflammatory response in the Achilles tendon complex compared to the patellar tendon of the ovariectomized and hysterectomized animals, since transcripts for a number of "proinflammatory" genes are elevated in the Achilles tendon compared to the PT. However, this possibility may be at odds with the general perception that females exhibit more robust inflammatory and immune responses than males, due at least in part to estrogen effects [22]. Whether removal of an estrogen supply would alter the response pattern to neuropeptides remains to be ascertained, but the preliminary findings support the concept that tendon cells can be influenced by sex hormones.

Influence of Denervation on Tendon Cell Activity at the mRNA Level

If indeed the innervation of the tendon was a contributing factor to the normal maintenance of tendon function, one may also expect that denervation of the tissue would lead to alterations in the activity of tendon cells. Of course, this type of experiment is somewhat compromised by the muscle atrophy that would accompany denervation of extensive portions of the leg surrounding the Achilles tendon complex. Given this caveat regarding direct or indirect effects on tendon cell activity, in a pilot study a 0.5 cm section of the femoral nerve of the right leg of skeletally mature female rabbits was removed using a modification of the method described by Wyland and Dahners [25], and then the animals were sacrificed 6 weeks postsurgery. Control animals had a sham operation with the nerve exposed but not transected. At the time of sacrifice, the operated legs were examined, and the nerve was found to be still disrupted. The Achilles tendon and paratenon of the right leg of operated or sham-operated animals were removed, and then the tissue processed for mRNA analysis. The tendon tissue was divided into the myotendinous junction (MTJ), the midsubstance (MS), or the insertion (INS) prior to processing so as to assess the uniformity of any changes occurring. Overt atrophy of the muscles associated with the Achilles tendon complex was uniformly evident.

As shown in Table 6-2, 4 of the 9 genes assessed had depressed levels in the MTJ following denervation, 1 of the 9 genes had an elevated level in the INS, but the influence of denervation on the midsubstance (MS) was nonexistent for the limited set of genes assessed. The effect of denervation on the paratenon, the most highly innervated part of the Achilles tendon complex, was also very modest, with TNF mRNA levels elevated and COX-2 levels depressed. Therefore, denervation did not appear to lead to extensive changes in the tissue, and, because of the muscle atrophy, changes detected might be due to indirect mechanisms. Another limitation of the protocol is that the tendons were not "stressed" in the denervated animals. Thus, some aspects of neuroregulation may only become apparent, or be accelerated, when the system is subjected to a stressor such as repetitive motion or excessive loading. While a different model was used, such an effect has been reported for plantar ulcer formation in denervated rats [26].

Table 6-2. Influence of denervation on mRNA levels in the rabbit Achilles tendon

	Achilles tendon			
Gene	MTJ[a]	MS	INS	Paratenon
Col I[b]	↓[c]	—	—	—
Col III	↓	—	—	—
Decorin	↓	—	—	—
COX-2	—	—	↑	↓
iNOS	—	—	—	—
TNF	—	—	—	↑
IL-1	—	—	—	—
UK	↓	—	—	—
MMP-13	—	—	—	—

[a] MTJ = myotendinous junction; MS = midsubstance; INS = insertion.
[b] Col I = Collagen I; Col III = Collagen III; COX-2 = cyclooxygenase-2; iNOS = inducible nitric oxide synthase; TNF = tumor necrosis factor; IL-1 = interleukin-1; UK = urokinase; MMP-13 = matrix metalloproteinase-13.
[c] Indicates effect of denervation on mRNA levels compared to sham operated age-matched controls.

Influence of Histamine on mRNA Levels in Tendon Explants

As discussed earlier, and depicted in Figure 6-1, one possible route for neurogenic influences on tendon tissue is via an effect of such peptides on resident mast cells in the tissues [27]. Upon stimulation by neuropeptides, the mast cells could release either preformed granule-associated components (i.e. histamine) or newly synthesized molecules (i.e. prostaglandins and leukotrienes). Connective tissue mast cells, but not mucosal mast cells, can be stimulated by neuropeptides such as SP [28]. Furthermore, mechanical stimulation can also result in partial degranulation of mast cells, so chronic repetitive motion could lead to the release of some mediators from mast cells. Interestingly, experimental vibration of the forearm of a male with carpal tunnel syndrome developing after occupational exposure to vibration led to increased plasma histamine levels in the affected forearm, and this was accompanied by localized angioedema [29].

It is also of interest that patients with scleroderma, a systemic autoimmune disease characterized by excessive fibrosis of skin and other organs [30], also frequently exhibit tendon changes consistent with fibrotic involvement and carpal tunnel syndrome [31–33]. An early stage of scleroderma can be an edematous phase [34], and mast cell stabilizers such as ketotifen and sodium cromoglycate can alter the disease course, at least in some patients [30,35–38]. The number of connective tissue mast cells is elevated in scleroderma skin during the edematous phase, but they decline significantly in later phases [34]. Therefore, once the disease has progressed past the early edematous phase and proceeded to the progressive fibrotic stages, mast cell stabilizers may be less effective, but this remains to be clarified, since mast cells have also been implicated in fibrotic conditions [39]. Recently, a patient with rapidly progressive scleroderma with pulmonary fibrosis was treated with ketotifen and he experienced an improvement in pulmonary function [Fritzler and Hart, unpublished].

Based on the above information and our interest in determining whether tendon explants were responsive to mast cell components in vitro, experiments were undertaken to assess the responsiveness of rabbit Achilles tendon and paratenon, as well as patellar tendon, to histamine in the above-described explant system. While many of histamine's effects are mediated at the level of the microvasculature/endothelial cell [40], histamine may influence endogenous fibroblast activity directly. Therefore, explants of Achilles tendon midsubstance and paratenon, as well as patellar tendon, from female rabbits were cultured for 24 hours +/– histamine (10^{-5} to 10^{-9} M). The tissue samples were then processed for mRNA level determination using semiquantitative RT-PCR [15,16,41].

As shown in Table 6-3 (Panel A), exposure of paratenon tissue to histamine did not influence mRNA levels for a subset of molecules that are known to participate in inflammatory reactions (COX-2, iNOS, TNF, UK). Expression of MMP-13, a matrix metalloproteinase expressed in rabbit tissues early after injury [42], was not detectable in these tissues, and expression was not altered following exposure to histamine. Similarly, MMP-1 mRNA levels were also not altered following exposure to histamine, but MMP-3 mRNA levels were elevated. In contrast, exposure of Achilles tendon midsubstance tissue to histamine lead to decreases in mRNA levels for all of the molecules assessed except MMP-1 and MMP-3. In the patellar tendon tissue exposed to histamine, only mRNA levels for COX-2, UK, and MMP-3 were depressed. While the direction of these changes was to a certain degree unexpected, the results do indicate that tendon tissue may be responsive to mast cell-derived histamine *in vivo*.

As indicated, the rabbits used in the above experiment were females, and it was possible that estrogen could influence the responsiveness of the tendon tissues to histamine. Therefore, the experiments were repeated with tissue from 7-month-old animals that had been subjected to ovariectomy and hysterectomy prior to sexual maturity (2 months). As shown in Table 6-3 (Panel B), and in contrast to the normal age-matched females (Panel A), exposure of the paratenon tissue to histamine now led to a decrease in mRNA levels for COX-2, UK, MMP-1 and MMP-3. Exposure of Achilles tendon midsubstance tissue to histamine led to decreases in mRNA levels for iNOS, TNF, UK, MMP-1, and MMP-3, but not COX-2.

Table 6-3. Effect of histamine on mRNA levels in tendon tissue from normal and ovariectomized + hysterectomized rabbits

	Achilles tendon		
Gene	Paratenon	Midsubstance	Patellar tendon
Normal[a]			
COX-2[c]	—	↓[d]	↓
iNOS	—	↓	—
TNF	—	↓	—
UK	—	↓	↓
MMP-1	—	—	—
MMP-3	↑	—	↓
Ovariectomy + hysterectomy[b]			
COX-2	↓	—	—
iNOS	—	↓	—
TNF	—	↓	↓
UK	↓	↓	—
MMP-1	↓	↓	—
MMP-3	↓	↓	↓

[a] Normal 7 month old females.
[b] Surgically altered at 2 months and sacrificed at 7 months of age.
[c] COX-2 = cyclooxygenase-2; iNOS = inducible nitric oxide synthase; TNF = tumor necrosis factor; UK = urokinase; MMP-1 = matrix metalloproteinase-1; MMP-3 = matrix metalloproteinase-3.
[d] Indicates change in mRNA levels following 24 hours *in vitro* exposure to histamine in explant cultures.

Exposure of patellar tendon tissue from estrogen-deprived rabbits to histamine led to a decreases in mRNA levels for TNF and MMP-3, but responsiveness at the level of COX-2 and UK mRNA was lost (Table 6.3). Thus, ovariectomy and hysterectomy appears to lead to changes in the pattern of responsiveness more in the Achilles tendon paratenon rather than the Achilles tendon midsubstance. As changes were also noted in the patellar tendon tissue responsiveness pattern after removal of estrogen-producing tissues, the findings are not unique to only one tendon/tendon complex. Whether other tendons (i.e., flexor tendons, extensor tendons, etc.) also exhibit unique estrogen-dependent patterns of responsiveness remains to be elucidated. Such information, plus the previously described effects of ovariectomy and hysterectomy, may be relevant to development of tendinopathies in postmenopausal women vs. younger women. In addition, some reports have indicated that oral contraceptive use, hormone replacement therapy, or gynecological surgery may be risk factors in tendinopathy and carpal tunnel syndrome development [43–45]. Therefore, the involvement of estrogens, as well as potentially androgens, and hormone-dependent events in the regulation of tendons under normal conditions and under stress environments should be evaluated in more detail.

While the above-described experiments support the concept that mast cell products can influence tendon cell activity, based on the results obtained thus far the mast cell product histamine would appear to be more of an anti-inflammatory mediator rather than a proinflammatory stimulus. Thus, in all tissues examined, exposure to histamine led to a decline in mRNA levels for molecules generally considered to be proinflammatory (i.e., COX-2, TNF) rather than an increase. In addition, most of the effectiveness in tissue from intact animals appeared to be in the Achilles tendon midsubstance, a part of the tissue with a paucity of mast cells, innervation, and microvasculature. However, if the Achilles tendon midsubstance was exposed to histamine released from mast cells in the paratenon, then the consequence of depressing levels for "proinflammatory" molecules could lead to an inhibition of some aspects of the repair process in this tissue. Sonographic evidence has shown that athletes with chronic tendinosis (midsubstance alterations) exhibit more microtears than do asymptomatic individuals, possibly indicating that repair processes are not activated in the symptomatic individuals [46]. Histologic analysis of tissue from patients with established tendinopathies (usually obtained at the time of surgery) often do not show evidence for inflammation [47], but may show edema [48]. Interestingly, exposure of macrophages to mast cell granules has been reported to lead to inhibition of iNOS and TNF mRNA levels [49], but this may be due to mediators other than histamine.

Assessment of mRNA levels for additional molecules (i.e., matrix molecules, growth factors, matrix metalloproteinases, TIMPs) will be necessary to determine whether the results obtained thus far are due to a general depression of metabolism in Achilles tendon midsubstance by histamine exposure, or whether it is selective, and mRNA levels for only a subset of molecules are affected. The results from the paratenon and patellar tendon experiments would be consistent with the histamine effect being selective, but further experimentation will be required before solid conclusions can be formed.

The finding that histamine can affect cell activity in tendon tissue is a first step, but histamine is only one of the potent mediators that mast cells can release into the extracellular environment. Others include growth factors, leukotrienes, prostaglandins, heparin, chemotactic factors, and proteinases [50–54]. Thus, while histamine in isolation has been shown to influence tendon cell activity *in vitro, in vivo* it is only one component in a complex milieu. Additional investigations with other mediators (alone or in combination) are required to determine whether other mast cell components affect tendon and paratenon cells in a manner different from those detected for histamine. As it is possible to isolate mast cell granules, it should be feasible also to investigate the impact of preformed mediators on tendon cell activities. However, such an approach would not account for those mediators produced by mast cells after stimulation by neuropeptides.

Is There a Relationship Among Neuromodulation, Sex Hormones, and Mast Cells That May Be Relevant to Tendinopathies?

The above-described studies indicate that sex hormones such as estrogen, pregnancy-associated factors, neuropeptides, and mast cell components such as histamine can impact on the activity of cells in tendons. One question that arises from such diverse information is "Are there any potential linkages between these avenues of study?" A review of the literature has revealed a paucity of information in this regard with respect to tendons specifically. However, some information derived from other tissues and species may indicate there are some "linkages" between these apparently diverse systems. In the rat, it has been reported that there are gender differences with regard to neuromodulation of mast cells in the rat intestine [55]. Also in the rat, mast cell number and apparent activation state can be influenced by the estrous cycle and pregnancy [56]. Furthermore, the pregnancy-associated hormone relaxin has been reported to inhibit mast cell degranulation in the rat heart [57]. Thus, neuromodulation, the mast cell system, and sex hormones appear to be regulated in an inter-dependent manner, at least in the rat. There also appears to be a relationship between mast cells and the nervous system, which may be involved in disease development in these tissues [58]. It remains to be determined whether such relation-

ships exist in tendons, and whether they contribute to the development and/or progression of tendinopathies. However, as many biological systems are conserved with regard to regulatory mechanisms, this may be a fruitful area for study.

Recent Advances

Since the present chapter was written, advances in some aspects of tendinopathies have appeared in the literature, as have some additional reviews of the field. With regard to the latter, a recent excellent review by Riley [59] discussed some of the molecular aspects of tendinopathies, while Paavola et al. [60] has reviewed the role of glucocorticords in the treatment of tendon disorders and Gill et al. [61] have reported a safety study of their use. Maffulli et al. [62] have reviewed the types and epidemiology of tendinopathies. In addition, Almekinders et al. [63] have discussed some of the potential etiological factors that may contribute to the development of tendinopathies.

In more specific areas of our understanding of tendinopathies, Corps et al. [64] have reported alterations in the splice variants of versican mRNA (a large aggregating proteoglycan) present in normal human Achilles tendon versus tissue from patients with tendinopathies. Similarly, Fenwick et al. [65] have reported that the isoforms of the growth factor TGF-beta and its receptors present in normal and tendinopathy tissue are different. It remains to be determined whether these findings are related to cause or effect in the tissues, and whether they may be involved in an attempt to repair the tissue. Yuan et al. [66] have discussed the potential role of cell death by apoptosis in development and progression of tendinopathies, but again, cause-and-effect relationships have not been established. However, loss of cells in the affected tissues would likely compromise the ability of the tissue to repair itself endogenously, and if exogenous cells were attracted to the site, this would likely result in formation of scar tissue that could provide some function. In an attempt to alleviate symptoms and stimulate repair of affected tissues, Murrell's group has also investigated the use of glyceryl trinitrate [67] in the treatment of human Achilles tendonopathy and reported some efficacy. The use of this compound was based on the effectiveness of nitric oxide related compounds to modify repair processes in animal models.

Therefore, progress is being made in some areas regarding our understanding of some aspects of the environment in an affected tissues and how it differs from "normal," as well as initial attempts to stimulate repair of the tissue. However, while these studies are highly relevant as most utilize human tissues, we are still lacking in understanding the molecular, cellular and genetic contributions to the development of tendinopathies and the interrelationship between the biology and the biomechanics operative in different tendons.

Summary and Future Directions

Obviously, the information discussed in this chapter is not complete, and one cannot yet formulate solid conclusions at this point. However, the results support the concept that tendons can potentially be regulated at the level of neuropeptides found in nerves terminating in tendons, at the level of sex hormones and pregnancy, and by mast cell products. The impact of these regulatory systems on the paratenon and tendon of a specific tendon complex (i.e. Achilles tendon) may be different, and the impact and interrelationships between these regulatory systems may differ between tendons in different environments where they are subjected to different loading parameters. As the incidence of tendinopathies in all workers in an occupation is not 100%, and all athletes in a particular activity do not develop tendinopathies, there must be other factors (such as biomechanics, genetics, anatomy, and possibly other conditions [atopy/allergies?]) involved in the development of the conditions. The regulatory systems described in this chapter likely modulate or influence the development of tendinopathies, but whether they are primarily involved in development of the conditions or they are secondary influences must await further investigation.

There are few animal models of overuse and repetitive motion syndromes leading to tendinopathy. Therefore, can we apply the above information to human tendinopathies to not only improve the quality of life for patients, but also gain additional information regarding possible mechanisms involved in the conditions? With regard to mast cell involvement in early disease, particularly paratendinopathy, it may be possible to test the efficacy of mast cell stabilizers on symptoms and disease progression in patients. If the early phase of such conditions are edematous, they may impacted by such drugs in a positive manner. Many of these are FDA approved for use in humans, and have been used in the treatment of other conditions for years. Therefore, this would be a new indication for an established family of drugs. As with their application in diseases such as scleroderma, the drugs may be effective primarily early in the disease, and therefore it would be important to identify potential patients very early after onset of symptoms. This obviously may complicate interpretation of efficacy, since some of these conditions could resolve without treatment. However, the incidence of conditions such as early carpal tunnel syndrome is quite high, so defining an appropriately designed clinical trial should be possible.

Recent investigations showed tendons from patients with chronic painful tendinopathies have significantly higher concentrations of glutamate, but not PGE2, as compared to the pain-free normal tendons. Glutamate might be involved in chronic tendon pain, and there is no chemical inflammation (normal PGE2 levels) in the chronic stage of common tendinopathies. The findings of glutamate and its receptors might have implications for treatment and be a potential target for drugs [68, 69].

Attempts to identify the role of sex hormones and neuromodulation in tendinopathy development and progression will be somewhat more difficult in human populations, and progress in these areas likely will depend on the availability of validated animal models. As discussed earlier, a number of models have been reported, but whether these are good models of human disease is still a controversial question.

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7
Imaging of Tendon Ailments

Tudor H. Hughes

Introduction

Twenty-five years ago, imaging of tendons was confined to faint soft tissue opacities on conventional radiographs, possibly with the visualization of calcification, and to tenography to show the surface anatomy of tendons and tears. Since then, there has been an enormous leap forward with the development of ultrasound (US) and magnetic resonance imaging (MRI). The fine internal architecture of the tendons can now be visualized by both of these methods, and their development continues apace. This chapter will concentrate on these later two methods. Local availability and experience are other major factors determining the choice of imaging modality. Also, the referring physician's comfort zone with the report of a dynamic study such as ultrasound may be a factor.

Conventional Radiography

Although the presentation of most tendon injuries will be clinically obvious, there will always be the unusual presentation. Because of this, conventional radiography is a good first line investigation since it is widely available, cheap, quick, and well understood by many. It can help to exclude significant other pathology such as a bone tumor presenting as a tendon injury, or show the soft tissue calcification of a variety of other conditions. In the immature skeleton, an apophyseal avulsion will occur rather than a tendon rupture, and conventional radiography will exclude this [1]. It may show direct or indirect signs of tendon pathology and is complimentary to other imaging techniques.

When looking for tendon pathology, it is important to adjust the conventional radiographic technique to enhance soft tissue and radiographic contrast. Patient positioning is important to reduce the amount of non-essential overlying tissue, which would decrease tissue contrast. Radiographic contrast can be enhanced by the use of a low kV. Fine focal spot size and fine grain single emulsion film will enhance detail. Exposure to ionizing radiation is always an issue, and low kV techniques increase the absorbed dose. However, most tendons imaged are in the periphery and through relatively thin areas of the body, where reduced exposures are used and the tissues are less sensitive to radiation. An experienced radiographer will produce reproducible high quality studies with the need for fewer repeat films.

There are essentially only four densities visible on radiographs: air, fat, soft tissue, and calcium. Visualization of a structure therefore depends on the contrast between these. For instance, calcification can be seen in soft tissue. A tendon that is normally clearly seen due to adjacent fat may no longer be visible if the fat becomes edematous and takes on the density of soft tissue. This can be a secondary sign of other pathologies such as scaphoid fracture with the loss of the fat plane between this and abductor pollicis longus and extensor pollicis brevis tendons [2], or indicate primary tendon pathology (Figure 7-1).

Radiographic signs of tendon pathology may be direct or indirect. Direct indicators would include calcification and thickening of the tendon (Figure 7-2). By obtaining both internal and external rotation views of a site such as the greater tuberosity of the humerus, the location of calcific deposits can be accurately assessed.

An indirect indicator of tendon pathology in a location such as the shoulder would be the reduction in the acromiohumeral distance to less than 6 mm. This is a good indication of a long-standing full thickness supraspinatus tendon tear, and, in some clinical settings, this will obviate the need for further imaging. Other indirect signs of tendon pathology would include the bony changes seen at tendon insertions, such as the bony pitting at the greater tuberosity suggesting long standing rotator cuff degenerative pathology. Radiography may show bony changes adjacent to tenosynovitis, such as periosteal new bone or cortical irregularity of the radial styloid in de Quervain's tenosynovitis [3]. Sometimes the presence of

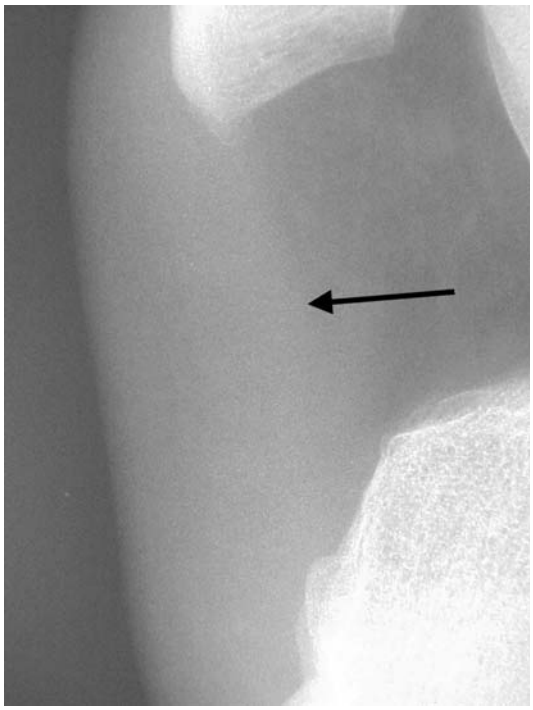

Figure 7-1. Lateral X-ray of the patella tendon. Loss of definition of the fat planes about the tendon due to paratendinosis (arrow).

an accessory ossicle can be an indicator of tendon problems, such as an accessory navicular and insertional tears or peritendinitis of the posterior tibial tendon [4].

Contrast Techniques: Tenography, Conventional Arthrography, and Bursography

The injection of water soluble contrast agents into tendon sheaths, joints and bursae is a relatively quick and safe way to outline these spaces and adjacent structures (Figure 7-3). Ironically, this is often easier under ultrasound control. These structures can then be imaged either statically with conventional radiography, or dynamically with fluoroscopy. Alternatively, the addition of dilute gadolinium can make an MRI-specific contrast agent, which can be very useful to assess structures such as the rotator cuff when injected into the glenohumeral joint (Figure 7-4). Distinction of this fluid from subdeltoid bursal inflammatory fluid that does not contain gadolinium makes it possible to confirm full thickness tears of the rotator cuff and accurately outline their margins. These injection techniques can be combined with therapeutic corticosteroid injections for inflammatory conditions, being particularly appropriate about the ankle [5]. The role of these techniques in isolation has been surpassed by MRI and US when available.

Computed Tomography

Despite huge advances in CT technology in recent years, principally due to computing power, its role in the imaging of tendons is very limited. Even reports 10–12 yeas ago already showed ultrasound to more accurately assess pathology [6,7]. US and MRI have better soft tissue contrast without ionizing radiation, and are preferable. CT may have a role in detecting small areas of calcification deep in soft tissues, such as along the linea aspera at gluteus maximus insertion or in the longus colli muscles and tendon in the cervical spine.

Nuclear Medicine

By the injection of the bone seeking, gamma ray emitting, radiopharmaceutical agent Tc-99 methylene diphosphonate, it is possible to study the entire skeleton with either planar or cross sectional (SPECT) imaging. Resolution is low, but the bone uptake reflects function. Areas of increased bony uptake may be seen adjacent to tendon

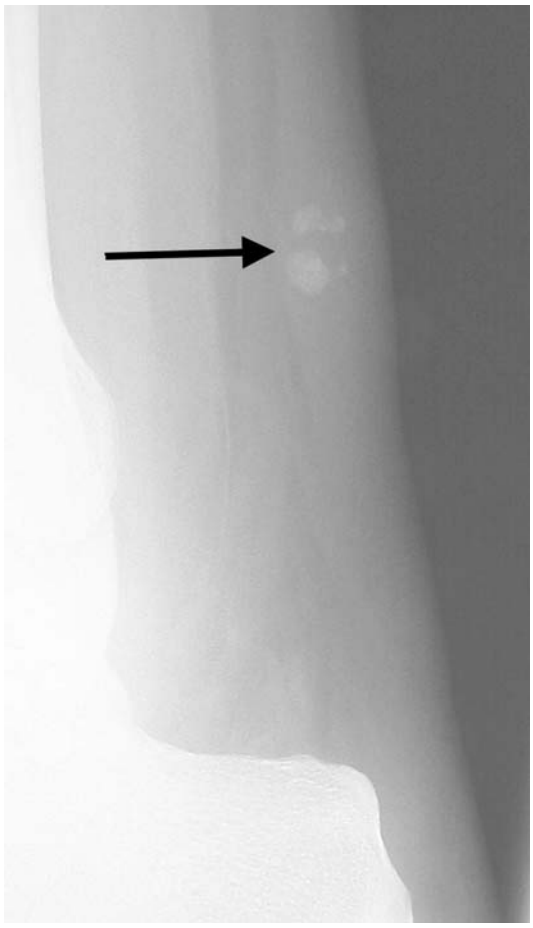

Figure 7-2. Lateral X-ray of the Achilles tendon showing the thickening of chronic tendinopathy and dystrophic calcification (arrow).

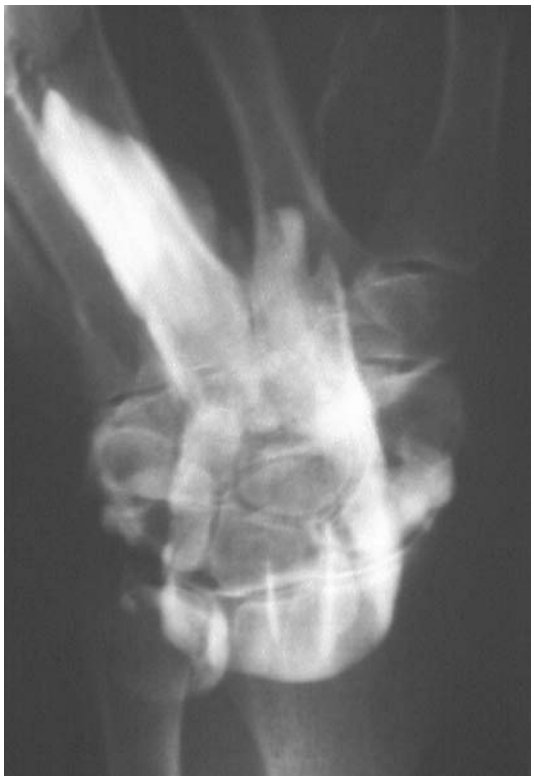

FIGURE 7-3. Iodinated contrast injection outlining the tendons in the common flexor sheath of the hand.

pathology such as the apophyseal insertions. It is also possible to see increased uptake in tendon calcific deposits (Figure 7-5), but, since these can also be seen with non-ionizing techniques, it is not justified.

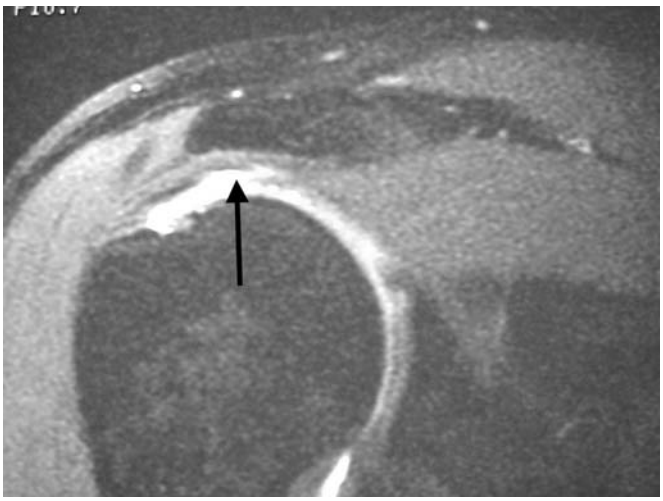

FIGURE 7-4. Coronal T1 fat saturated image of the right shoulder following intraarticular injection of dilute gadolinium. Undersurface partial thickness supraspinatus tendon tear (arrow).

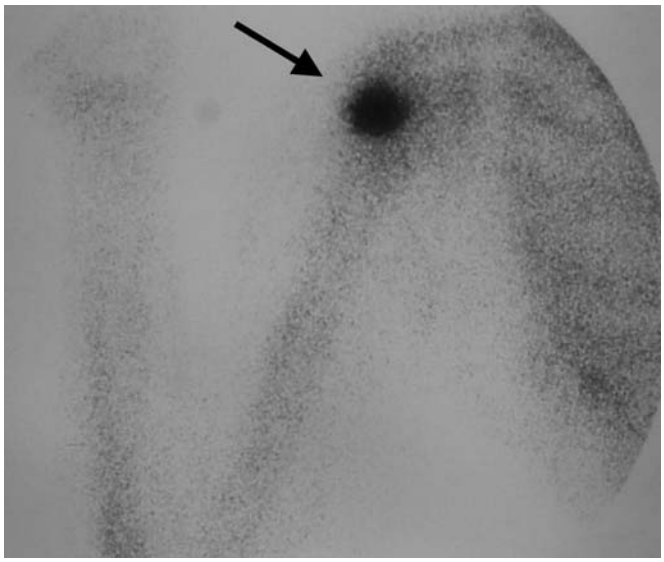

FIGURE 7-5. Methylene diphosphonate delayed phase bone scintigraphy of the right shoulder, showing abnormal uptake due to calcific tendonitis (arrow).

Ultrasound

Ultrasound imaging of tendons has recently become a first line investigation as it is widely available, relatively inexpensive, easy to use, and gives high lesion detection. There have been tremendous advances in ultrasound technology, making many of the older machines and probes inadequate for the imaging of tendons. Recent advances include higher frequency (10 to 15 MHz) broad bandwidth probes, with better near field beam focusing and gray scale processing, giving very high resolution near field imaging. (Ultrasound has better than twice the resolution of MRI [8] in the axial plane.) Doppler shift color imaging and, more recently, power Doppler imaging to detect flow have become essential adjuncts to gray scale imaging in the assessment of vascularity. This is particularly important when assessing inflammation and tumors. More recently, harmonic imaging and contrast agents have been introduced, to produce higher resolution in deeper structures, and increased detection of flow. Compound (Sono CT) (Figure 7-6) imaging has recently been introduced, and, although not essential to reduce artifact of curved anisotropic structures (see below), it makes the process far easier, and likely reduces false positive results. 3D imaging is also now available, but of limited use in tendon imaging. Also, very recently introduced is panoramic imaging, which uses very powerful computing techniques, to seamlessly combine images and produce panoramic views of structures which extend beyond the normal field of view (Figure 7-7). This is very useful for showing the relationship of one structure to another, such as a musculotendinous junction tear of the Achilles to the calcaneus. US does have the advantage of

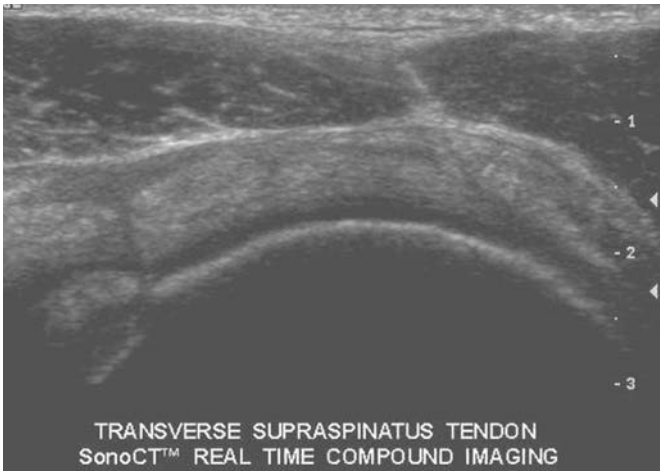

FIGURE 7-6. Transverse compound ultrasound of normal supraspinatus. Anterior is on the left of picture.

rapid comparison with the contralateral corresponding tendon, and of dynamic imaging.

Ultrasound of tendons requires a great deal of experience, and is operator dependent. (Both MRI and US are operator dependent [9].) With experience, there is good interobserver correlation when looking at rotator cuff pathology [10]. One of the key issues of ultrasound is that it is a hands-on procedure with the patient. The area of pain can be interrogated and the relevance of the findings put into clinical perspective. This is particularly important, since US, like all imaging modalities, will find abnormalities that are of no clinical significance.

With regards to lesion detection, there are now numerous studies, which generally show good accuracy for US. Depending on the area of interest, US and MRI usually have similar detection rates for a variety of pathologies. Due to near field resolution, US is often better for superficial structures and MRI better for deeper structures [11].

The appearance of tendons with US is determined by their anatomy. Interfaces that run parallel to the surface (footplate) of the probe (right angles to the line of insonation) produce strong specular echoes. Hence, if a tendon runs parallel to the surface of a linear probe, not only will the epitendineum surrounding the tendon produce a strong bright echo, but so will the internal fibrillar bundles of collagen. As the transducer frequency increases, these internal linear echoes derived from the interfaces of collagen bundles and interleaving loose connective tissue increase in intensity and become thinner, producing a fibrillar pattern. Because of the ordered parallel nature of tendons they are anisotropic (different properties in different directions). Obliquity of the tendon produces areas of reduced echoes. This can occur if the probe used is a curved array rather than linear, or if the tendon is curved, such as the rotator cuff. This also commonly occurs at the bony attachment of a tendon when the fibers curve to enter the bone at an enthesis. This is most apparent at the Achilles and supraspinatus tendon insertions (Figure 7-8). Also occurring normally at these sites is a narrow zone of hyporeflectivity (dark) at the tendon-bone interface. If the tendon is not parallel to the skin, such as the distal insertion of biceps brachii, then a compressible triangular stand off can be useful to help angle the probe for the tendon and maintain contact with the skin. The uniform fibrillar pattern may also be broken when a tendon is derived from two or more muscles, such as the Achilles or quadriceps femoris tendons. This type of normal variant should not be mistaken for a longitudinal tear.

To enable the tendon to move through the surrounding tissues, the tendon either has a synovial sheath containing a thin film of lubricating fluid, or a paratenon composed of loose areolar and adipose connective tissue. A normal synovial sheath is seen at US to be a thin hypoechoic (dark) rim around the tendon, unlike the paratenon, which is an undefined hyperechoic (bright) rim. It is also normal to see an increase in the fluid around tendons that communicate with joints following exercise. Although this could be problematic to differentiate from pathological fluid, clinical and ultrasound correlation with other findings should help.

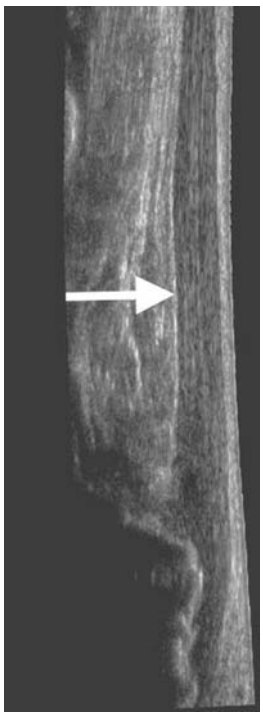

FIGURE 7-7. Sagittal panoramic compound ultrasound of the normal Achilles tendon.

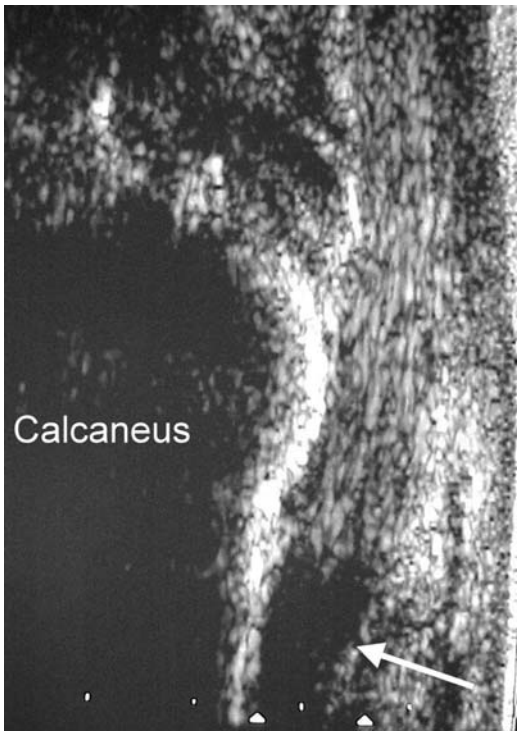

FIGURE 7-8. Non compound sagital ultrasound of Achilles tendon showing anisotropic artifact at the insertion onto the calcaneus (arrow).

The course of the tendon close to a joint is often constrained, by a bony tunnel, a groove, a retinaculum or an annular pulley. The soft tissue constraints may be difficult to see with US due to anisotrophy, but their disruption can be detected by both US and MRI either directly or by tendon displacement [12]. Bursae are often present when a tendon passes over a bony prominence. These can be seen with US and MRI and are usually less than 2 mm thick. As with synovial sheath fluid this can increase following exercise.

Magnetic Resonance Imaging

Some of the recent developments in MRI of tendons involve more dedicated surface coils for the various parts to be imaged, and new sequences to reduce the time, and increase the resolution and contrast. These faster scans reduce the risk of patient movement that would otherwise produce non-diagnostic images, and allow time for additional sequences to improve diagnostic accuracy. The use of fat suppression techniques and MRI-specific contrast agents are now commonly employed. MRI remains an expensive imaging modality.

The one great advantage of MRI over a technique such as US is that it gives a reproducible overview of the area of interest in multiple planes. Other possible non-tendon pathologies are also covered. When combined with Gadolinium arthrography of the shoulder, MRI can give a one step investigation of shoulder pain [13] (Figure 7-4). This is of particular value in the assessment of the long head of biceps anchor and the rotator cuff undersurface.

Some basic principles of the physics of MRI need to be stated. The way the scanner is programmed will determine which characteristics of the tissue are enhanced. A T1 weighted image gives good signal to noise ratio and is good for anatomy. A T2 weighted image has high signal (bright) from fluid, which is the common situation for most pathology. Fat is bright on T1 sequences which is useful to outline structures, and on the newer fast spin echo T2 techniques. This relatively high signal from fat obscures the high signal of pathology. Hence, many of the newer sequences use techniques to suppress the signal from fat.

Generally, normal tendons have a uniform low signal (dark) on both T1 and T2 weighted MRI. An artifact known as the 'magic angle artifact' can occur due to the highly organized longitudinal pattern of tendon [14]. This occurs when the tendon passes through an angle of 55 degrees to the main magnetic field. With T1 imaging the tendon may falsely appear bright. T2 imaging is not affected by this artifact and is used to differentiate the high signal seen on T1 due to magic angle from that seen in pathology (Figure 7-9). Another associated artifact occurs at bony entheses in a similar way to US, where a thin band of higher signal may be observed. In addition to looking for pathology in tendons, MRI can assess function. By a noninvasive method, the degree of myotendinous and tendon stretch can be measured and used as an indirect measurement of force production [15].

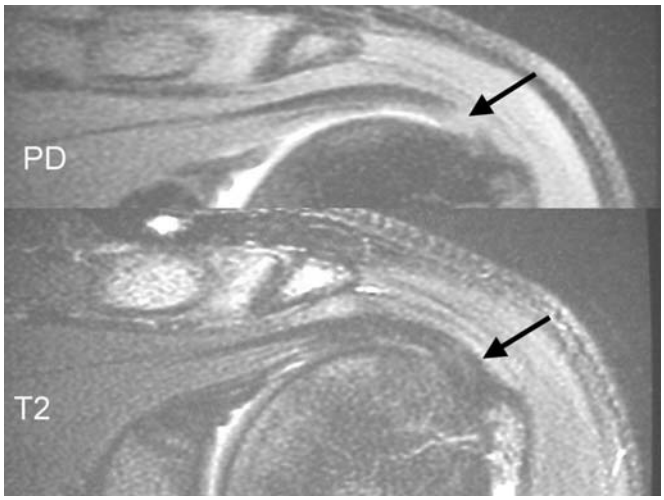

FIGURE 7-9. Coronal proton density (top) and T2 (bottom) MRI of the left shoulder. Magic angle artifact seen on PD is cancelled out on T2 (arrows).

US and MRI of Pathology

The common pathologies of tendons that US is used to image include degeneration and tears, dislocation, inflammatory conditions, and tumors.

Tendon Degeneration

The main difference between degeneration due to aging and chronic overuse degeneration is the presence of pain in the overuse syndrome (tendinopathy), although a small tear may cause pain in an aged degenerative tendon. Tendinopathy may also be due to a direct contusion or recurrent subluxation. The point of injury or the presence of US-detected subluxation are good pointers as to these causes.

Although an otherwise normal tendon may rupture due to a single significant traumatic event (Figure 7-10), many reports now suggest that there is a spectrum of conditions with multiple microtraumas producing degeneration in a tendon that may then progress to rupture with only mild trauma. Indeed, supraspinatus tendon rupture can be asymptomatic with no loss of strength [16]. Ultrasound of contralateral Achilles tendons to those ruptured may show significant thickening, which may indicate that tendinopathy predisposes to tendon rupture [17]. The role of overuse as a precursor to degeneration (tendinosis, tendinopathy) is not well understood. Ultrasound can differentiate the various stages of tendon damage, and may have prognostic significance.

The earliest change of tendinopathy is when the US and MRI show the tendon to be thickened (Figure 7-11). The diameter of ankle tendons does not change with the degree of ankle plantar or dorsi flexion, as shown by MRI [18]. The usually uniform fibrillar pattern may be reduced, more hyporeflective with US and heterogeneous, due to the deposition of glycosaminoglycans in the extracellular matrix, and the breakdown of collagen microfibrils. Internal increased signal on T1 and T2 images with fat suppression is observed (Figure 7-12). The use of contrast medium-enhanced T1 MRI does

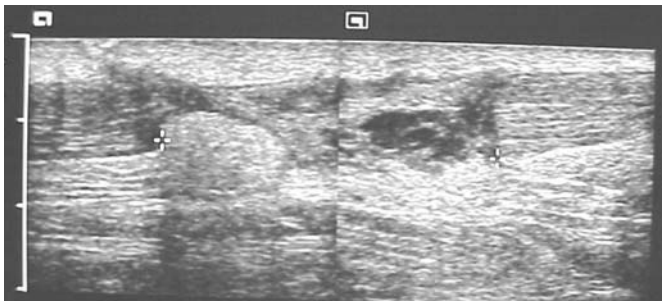

FIGURE 7-10. Sagital plane ultrasound of the Achilles tendon following a laceration injury with distraction of the tendon ends to the asterisks, in an otherwise normal tendon.

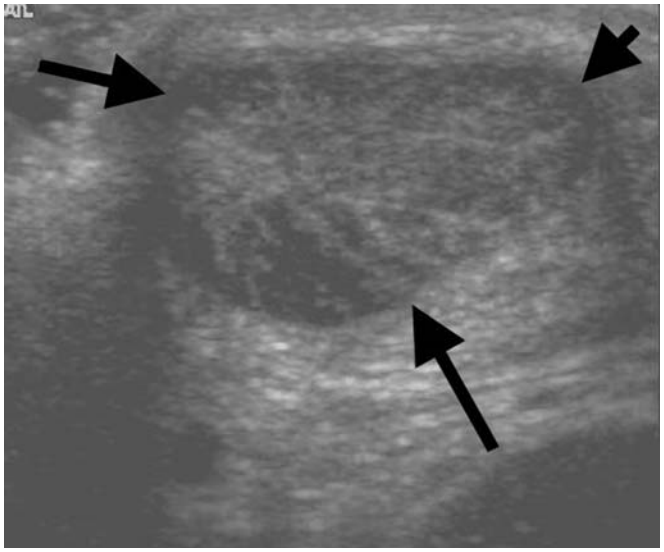

FIGURE 7-11. Transverse ultrasound of the Achilles tendon showing the marked thickening of tendinopathy (inside arrows).

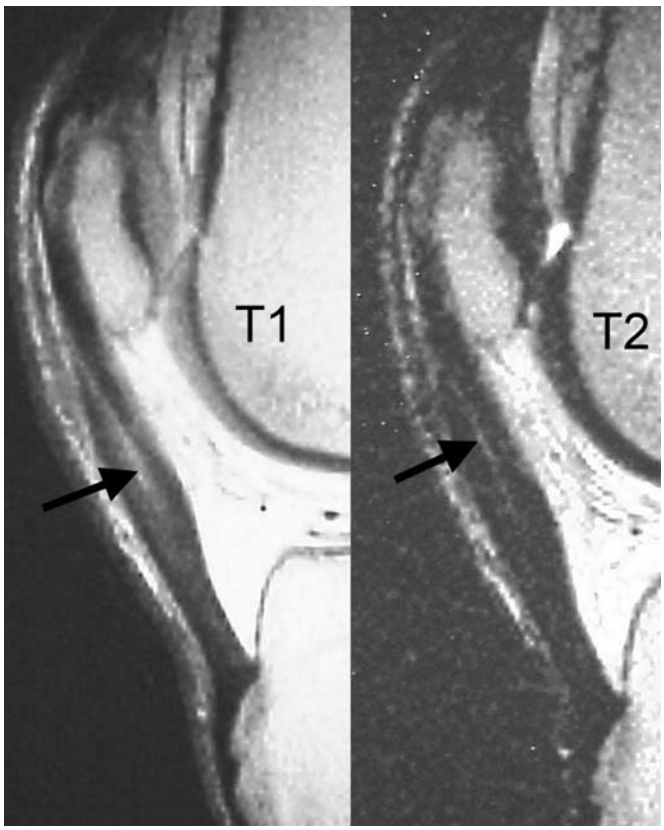

FIGURE 7-12. Sagital plane T1 (left) and T2 (right) MRI of the patella tendon. High signal in the proximal tendon represents myxoid change of chronic tendinopathy (arrows).

show abnormality in regions of the Achilles tendinopathy beyond that shown by US [19].

As this process continues, small cystic collections develop in the tendon. These are visible as focal hypoechoic regions, or high signal on T2 within the expanded tendon. Fibrocartilaginous metaplasia can occur in these areas of abnormal tissue, producing areas of calcification visible on both plain radiography and ultrasound scans, but often poorly seen with MRI. The abnormal configuration of the tendon can evoke a bursal effusion adjacent to points of constraint. Possible imaging findings that may suggest overuse tendinopathy rather than aging degeneration are the close correlation of imaging abnormalities and tenderness to US probe pressure. Also, there is increased intratendon and peritenon vascularity, which can be observed with color Doppler imaging but is better depicted by power Doppler imaging (Figure 7-13).

Other extratendinous changes, such as an accompanying thickening of the retinaculum, also point to a tendinopathy. The cause of pain with overuse tendinopathy may well come from the peritendinous inflammation since tendons do not possess nociceptive nerve fibers, but only stretch receptors. With overuse tendinopathy, mild bone marrow edema can be observed at the apophyses and in the peritendinous tissues on T2 fat suppressed images. MRI is accurate in the detection of overuse tendinopathy of the Achilles and the associated peritendinous changes that may occur [20].

MRI imaging of Haglunds syndrome not only shows the insertional tendinopathy, and both the retrocalcaneal and retro-Achilles bursitis, but also calcaneal tuberosity edema [21]. However, one group has suggested that both MRI and US do not offer sufficient diagnostic accuracy, when compared with clinical examination in the assessment of chronic injuries of the Achilles tendon [22]. Others have shown good correlation between both US and MRI with histologic changes in the proximal patella tendon of jumper's knee [23] and of Achilles tendinopathy [24,20]. With continuing breakdown of the collagen microfibrils, small tears occur and these can progress to complete rupture.

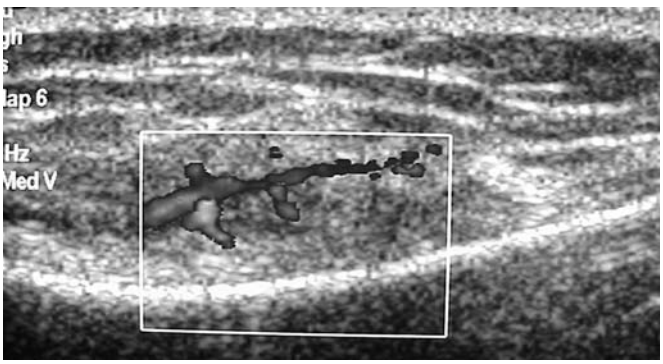

FIGURE 7-13. Coronal plane colour Doppler ultrasound of the pes anserinus tendon insertion. The increased colour flow in and around the tendon indicates a paratendinitis.

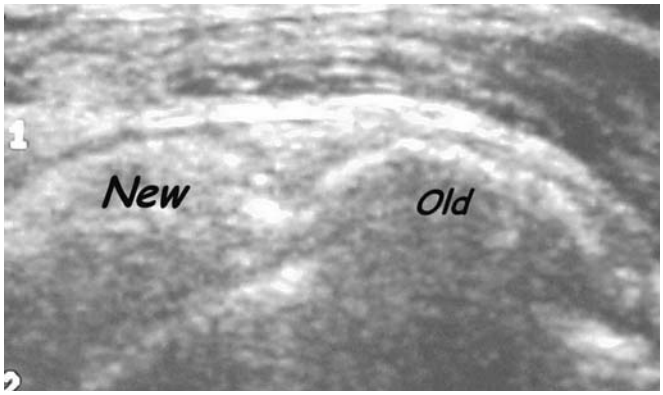

FIGURE 7-14. Transverse ultrasound of the supraspinatus tendon showing the different morphology of calcific tendinitis. The old calcium has a strong superficial spectral echo and deep shadow and is unlikely to drain via needle aspiration.

Crystal deposition disorders are another common association of chronic tendinopathy. In the acute stage of deposition, the crystals may be an amorphous hyperechoic mass without acoustic shadowing. This has fluid consistency and may deform, which suggests needle aspiration is likely to be successful, and could also be directly guided by the US [25]. When chronic, the mass has a strong punctate appearance and superficial spectral echo with deep shadowing, and is unlikely to drain via a needle (Figure 7-14). Crystal deposition can have high signal in the acute phase within the tendon on T2 images. MRI imaging of calcific tendinopathy of the hip shows associated inflammatory change and enhancement of the tendon and edema of the adjacent bone [26]. In the chronic stage, the signal is similar to normal tendon and the crystals can be difficult to see.

Another form of tendinopathy is xanthomatous deposition in states of hypercholesterolemia, particularly the familial forms. In this situation there is tendon heterogeneity, with multiple hypoechoic nodules in a thickened tendon. It is also usually bilateral. Xanthomatous deposits have high signal on T1 due to their fatty (cholesterol) nature.

Tendon Rupture

Nearly all tendon ruptures, either partial or full thickness, may be predisposed to by some form of tendinopathy mentioned above (Figure 15). Partial tears may be either longitudinal or transverse. The cardinal feature of partial or complete tendon rupture is the discontinuity of fibers (Figure 7-16). If retraction of fibers occurs, there will either be absence of the tendon or a contour defect of the surface. Because a variety of substances (fluid, fresh

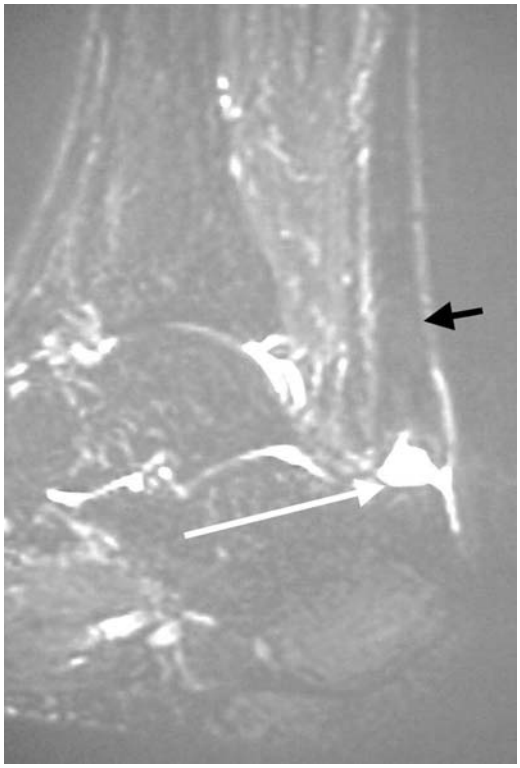

FIGURE 7-15. Sagital fat suppressed (STIR) image of the achilles tendon. The tendon is thickened (black arrow) compatible with chronic tendinopathy, and has an acute distal rupture (white arrow).

blood, organizing hematoma, granulation tissue or pseudotumor) can fill the tendon defects, the imaging appearances are variable. When long standing, the tears may calcify or ossify. It is therefore necessary to rely on the discontinuity of the fibers (excluding artifact as the cause) to make a diagnosis of tear. Tendon ruptures are seen with MRI as discontinuity of the normal tendon low signal, which is replaced by high signal on T2 weighted images (Figure 7-17). An acutely torn tendon is often associated with retraction and a hematoma collecting at the musculotendinous junction, which appears as a heterogeneous hypoechoic mass. MRI and US both have good accuracy for the detection of full thickness rotator cuff tears [27], but are less accurate in the detection of partial thickness tears [9,28]. A prospective study of US and MRI for tendon abnormalities about the ankle showed US to be much more accurate than MRI in the detection of intrasubstance and complete tendon tears [29]. Dynamic ultrasound and MRI show similar accuracy in the detection of longitudinal posterior tibial tendon surgically induced tears in cadavers [29,8]. MRI is also very good for the assessment of distal biceps tendon tears [30]. In addition, with chronic tendon tears MRI can detect the associated atrophy of the muscle with fatty infiltration, which takes on an appearance of marbling, and measure supraspinatus tendon retraction, which extends beneath the acromium (Figure 7-18).

These are two factors that determine surgical management. Ultrasound is not as good as MRI at assessing

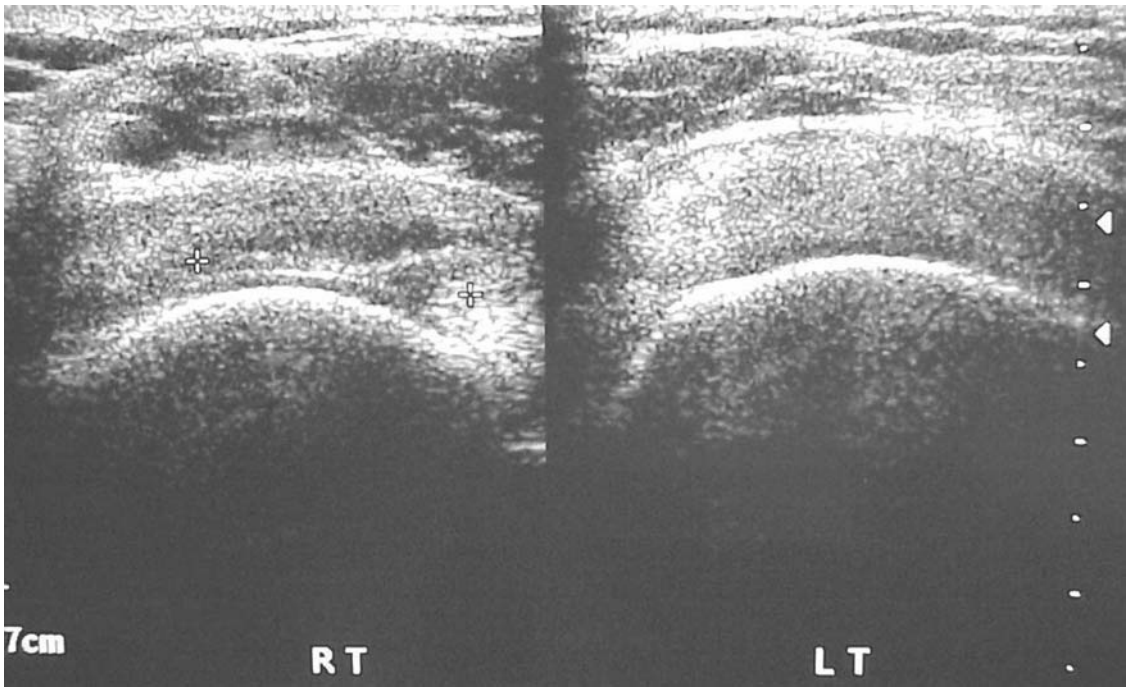

FIGURE 7-16. Transverse ultrasound of the supraspinatus tendon of both shoulders. The left is normal. The right has a full thickness tear between the astericks.

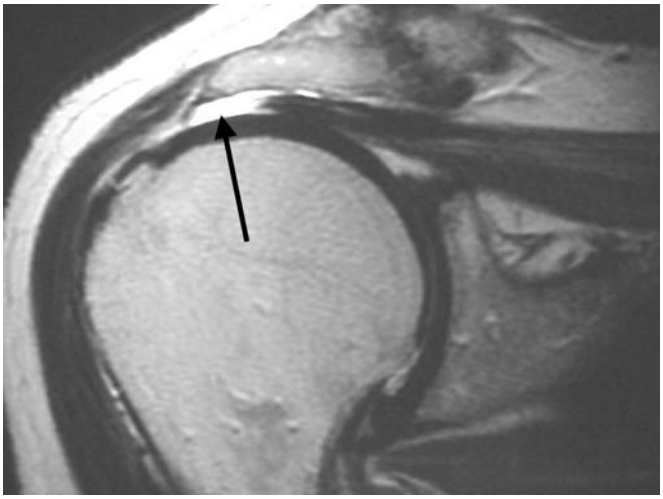

FIGURE 7-17. Coronal T2 MRI of the right shoulder. There is a full thickness tear of the supraspinatus tendon with fluid in the gap (arrow).

muscle changes secondary to chronically torn tendons, particularly muscles that pass deeply away from the probe such as subscapularis. MRI is likely superior to US in the assessment of postoperative repairs of the Achilles and may be prognostic for re-rupture [31]. MRI has limited ability to differentiate focal myxoid degeneration from partial tears of tendons, and US is superior in this matter [10].

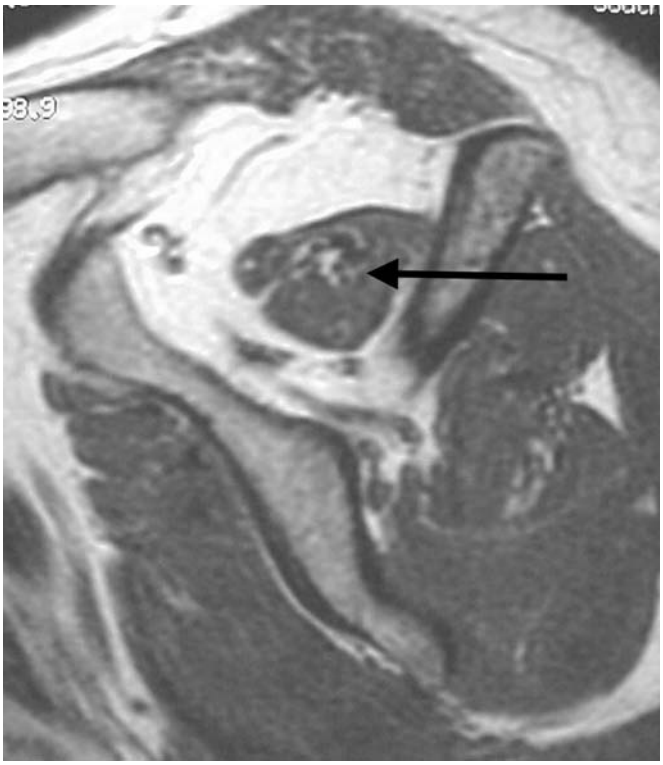

FIGURE 7-18. Sagital T1 MRI of the supraspinatus tendon. The muscle is atrophied and mildly marbled (arrow).

Tendon Dislocation

Dislocation of tendons occurs in tendons with a synovial sheath when there is disruption of the constraints. It is most commonly seen with the peroneal tendons, the long head of biceps brachii, and the flexor tendons of the hand. Disruption of the insertion of subscapularis can allow the long head of biceps brachii to dislocate medially from its groove (Figure 7-19), most commonly deep to subscapularis, but occasionally superficial. Either of these situations is well seen with US and MRI as an empty bicipital groove and displaced tendon. A pseudotendon due to granulation tissue within the groove can be misleading. Since US is a dynamic investigation it is also possible to observe biceps tendon subluxation with external rotation of the arm, which relocates on internal rotation. Dynamic US is also useful for peroneal tendon dislocation following rupture of the superior peroneal retinaculum. This is enhanced by dorsiflexion and foot eversion. As mentioned above a chronically subluxing tendon will show secondary degenerative change. Dynamic scanning with active finger flexion enhances subluxation of finger flexor tendons. All of these dislocations will have accompanying increase in surrounding fluid, either within the sheath, the bursa, or surrounding soft tissues. Tendon dislocation can easily be seen by MRI if the tendon is dislocated at the time of imaging. However, some tendon dislocations are joint position dependent and therefore the only signs may be interruption of pulleys or retinacula, or abnormal signal in the tendon.

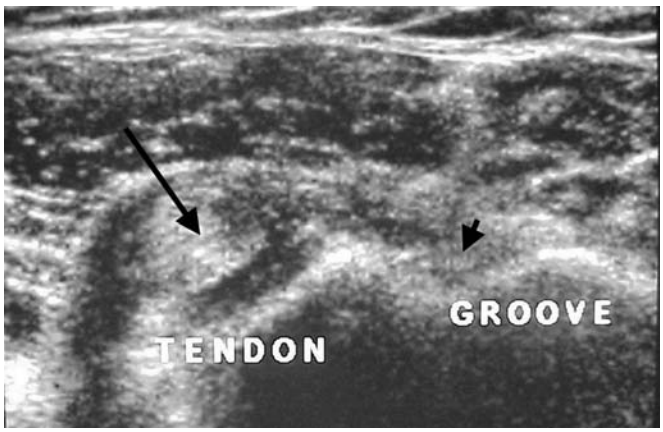

FIGURE 7-19. Transverse ultrasound of the left bicipital groove. The groove is empty (short arrow) and the tendon dislocated medially (long arrow).

Inflammation

The causes of inflammation of tendons include acute overuse syndrome, infection, and the inflammatory arthritides, most notably rheumatoid arthritis. The imaging appearances vary according to whether or not there is a synovial sheath. Usually there is thickening of the tendon that on US can be heterogeneous and hypoechoic.

When there is a synovial sheath, the hallmark finding on both US and MRI is fluid in the tendon's sheath and possibly thickening of the synovium, especially in tuberculous infection. On MRI, the thickened synovium is bright on T2 sequences and enhances post gadolinium on T1 sequences. The fluid varies from anechoic to hyperechoic when purulent. When the fluid appears complex, it is most likely due to pus or to the rice bodies of rheumatoid arthritis. When infectious, the adjacent tissues may show cellulitis and edema on both US and MRI. This is not pathognomonic, and aspiration will be required if infection is suspected. The hyperemia of inflammation can be seen, with both US and MRI, within the tendon, the mesotendon and synovium. Villous projections can be seen extending into the fluid from hypertrophic tenosynovitis such as rheumatoid arthritis and tendon rupture can be associated. US and MRI have good specificity but poor sensitivity for partial thickness finger extensor tendon tears in rheumatoid arthritis [33]. Doppler US will not only show the hyperemia, but can help distinguish hypoechoic hyperemic pannus from hypoechoic fluid, which can be useful to assess disease progression and response to therapy. MRI is useful to assess disease activity in rheumatoid arthritis [34]. Dedicated MRI sequences including MRA and post gadolinium T1 fat saturated images are exquisitely sensitive for early rheumatoid hyperemia (Figure 7-20).

When there is a paratenon rather than a synovial sheath, the peritendinous regions may become irregular and thickened with hyperemia. This is seen on MRI as poorly marginated high signal on T2 weighted images and on US as an irregular compressible fluid filled space. Adhesions of the tendon may also occur. Flow may be seen within the tendon, more so than those with sheaths. A stenosing tenosynovitis such as de Quervain's or trigger finger may occur at sites of tendon constraint. The thickened tendon can be observed with dynamic US passing through the thickened synovium at the points of entrapment

Tendon Tumors

The tumors and tumor-like conditions that can affect the tendon sheath complex include ganglion cysts, giant cell tumor of tendon sheath, fibroma of tendon sheath [35] and synovial sarcoma. They arise from the sheath.

Ganglion cysts are common peritendinous cystic lesions filled with mucoid material. They are common on the dorsum of the hand and foot. On ultrasound, they are hypoechoic or anechoic with through transmission of sound producing posterior acoustic enhancement (Figure 7-21). There should be no internal blood flow in contradistinction to a tumor and therefore Doppler should

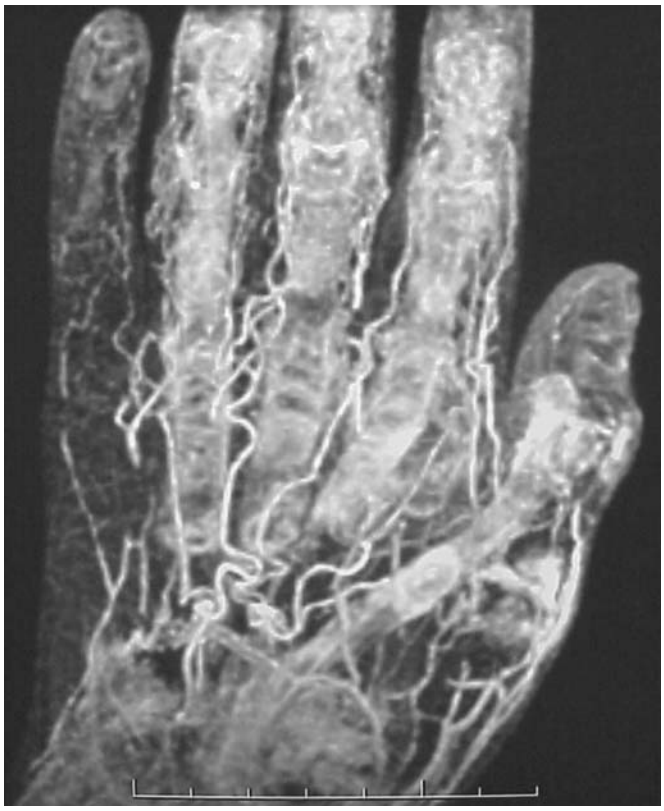

FIGURE 7-20. Late phase coronal maximum intensity projection of intravenous MR angiography. There is a generalised enhancement of the inflammed tendon sheaths. (Courtesy of David Connell, Melbourne, Australia.)

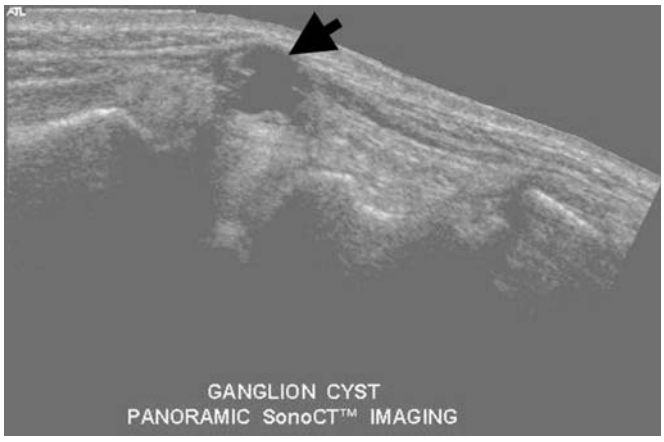

FIGURE 7-21. Panoramic sagital compound ultrasound of the wrist showing a ganglion cyst (arrow).

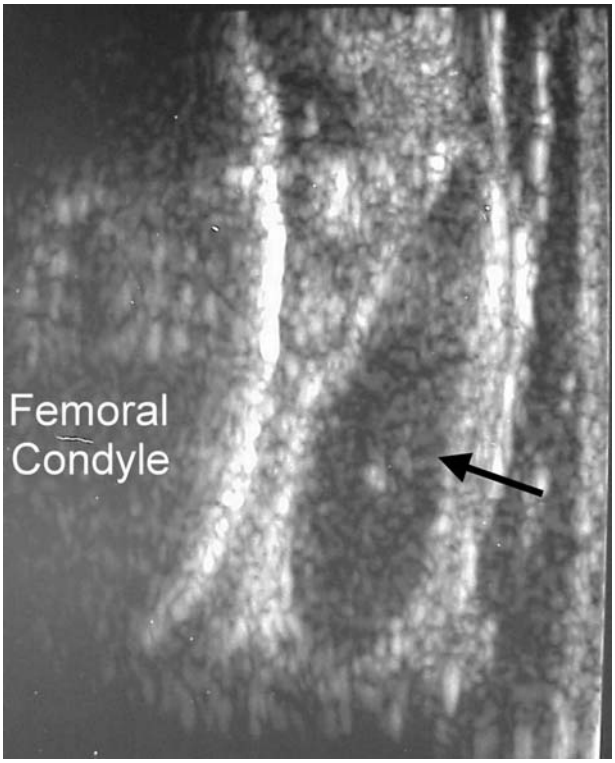

FIGURE 7-22. Coronal plane ultrasound of the lateral femoral condyle. The arrowed structure has deep acoustic enhancement suggesting a ganglion cyst, but internal echoes suggest a solid structure. Colour Doppler showed internal blood flow in this synovial sarcoma.

always be used, especially if there are any internal echoes (Figure 7-22). US and MRI are both good in the detection of dorsal carpal ganglia, but US is more cost-effective [36]. Those at the hip and knee are usually visible with US, but often stand out more clearly on T2 MRI as focal hyperintensities (bright).

Giant cell tumor of tendon sheath is a form of pigmented villonodular tenosynovitis (PVNS). These are more common on the volar aspect of the hand. US shows the mass to be hypoechoic with internal echoes but no posterior acoustic enhancement. They are well defined, close to a tendon and may show internal Doppler signal. They may have a characteristic appearance with MRI if hemosiderin is present and strongly enhance in a heterogeneous way [37,38]. They have a high local recurrence rate (not as high as PVNS of joints) and US can be used to detect early recurrence. MRI with contrast enhancement is relatively specific in the diagnosis of PVNS of joints, but less so with GCT of tendon sheath [38].

Fibroma [34] and synovial sarcoma of tendon sheath are rare. Like many other tumors, they appear as hypoechoic masses on US without posterior acoustic enhancement and with internal Doppler blood flow. On MRI they are of intermediate signal on T1, bright on T2 and when small show homogeneous T1 enhancement following intravenous gadolinium contrast agent, or more heterogeneous enhancement if larger due to central necrosis.

Conclusion

The exact roles of US and MRI in tendon imaging are still evolving [39,40]. A major factor is local availability and expertise. Europe [28] and Australasia [11] tend to employ US as a first line study, and North America tends to employ MRI [41]. The rebate for the study may be another factor. Conventional radiographs are a useful adjunct to both US and MRI. Both US and MRI show similar accuracy for most pathologies. Cost is a significant factor, and indicates that US should be the first line investigation for most tendon imaging. MRI has a role in equivocal cases.

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Part II
Anatomical Sites and Presentation

8
Injury of the Musculotendinous Junction

Jude C. Sullivan and Thomas M. Best

Introduction

People of all ages and levels of physical ability are innately dependent on the ability to move. Motion occurs in the frontal, sagittal and transverse planes. Muscles are orchestrated to either evoke movement or maintain dynamic stability via concentric, eccentric and/or isometric contractions. Yet, skeletal muscle itself is incapable of controlling movement unless it is connected to bone. Bones, and their associated joints, act as lever systems with muscle forces acting as the counterbalance to an applied load. However, a strong muscle alone is incapable of either supporting or overcoming a load. Muscle is dependent upon its connection to bone via tendons, and the boundary of this connection is highly dependent upon the integrity of the musculotendinous junction. This chapter describes the basic structure and function of skeletal muscle, and in particular the musculotendinous junction (MTJ). We will discuss MTJ injury and review current theories of inflammation and repair following MTJ stretch injury. Finally, we will review current training techniques implemented to reduce injury potential to the MTJ.

Muscle Structure and Function

Skeletal muscle comprises 40% to 50% of the total body mass. Unlike smooth or cardiac muscle, which are exclusively involuntary muscle structures directed by the autonomic nervous system, skeletal muscle is considered voluntary and is therefore predominantly influenced by the central nervous system. However, skeletal muscle also possesses sensory reflexive properties that help refine movement patterning and protect it from injury. The extracellular connective tissue framework that is responsible for support and protection provides organization that allows for optimal contraction efficiency resulting in force production and joint movement. Skeletal muscle is capable of simultaneously performing a number of functions including movement, temperature control and serving as a storehouse for various metabolic constituents. In fact, movement functions have been likened to more pragmatic terms such as “motor,” “spring,” “shock absorber,” and “stabilizer” [1]. Finally, muscle has a well developed capacity to adapt to environmental and training conditions.

Muscle Organization

All skeletal muscles are composed of many individual fibers that can be broadly categorized as fast twitch, fast twitch/glycolytic or slow twitch.

A single fiber is multinucleated and is surrounded by a plasma membrane known as sarcolemma. Each fiber has a characteristic banding appearance of alternating light and dark bands referred to as striations. When viewed microscopically, the lighter stripe is the I-band and the darker band is the A-band. The dense line that runs through the middle of the I-band is the Z-line. The central part of the A-band is the H-zone and it is bisected by the M-region. One sarcomere is the distance between successive Z-lines.

Individual muscle fibers vary in both thickness and length. The myosin filament is thick, and corresponds to the A-band. The actin filament is thin and corresponds to the I-band. In a resting muscle fiber, actin filaments overlap with myosin filaments. The region without overlap is the H-zone. The M-region forms the lattice that holds the myosin in position. The actin filaments surround each myosin filament hexagonally. The actin filaments are anchored by the Z-band without actually crossing it. Z-lines are maintained in relation to one another within a single muscle fiber by intermediate protein filaments and are anchored to the basement membrane and endomysial sheath surrounding the muscle fiber.

The connective tissue of skeletal muscle provides a lattice for force transmission to the tendon with resultant

joint rotation and motion. Most of the fibers possess immunologically distinct collagen types (I–V), with the remaining portion being elastin. This collagen network has 3 anatomical divisions:

Epimysium—a tough coat that covers the entire surface of the muscle belly.

Perimysium—another relatively thick coat that binds muscle fibers into fascicles. It also provides a path for major blood vessels and nerves to run through the muscle belly. Immediately beneath this is another, more delicate, network of collagen fibers connected to the endomysium.

Endomysium—lies external to the sarcolemma and surrounds each muscle fiber with collagen fibers.

Muscle is anchored to bone by a tendon and tapers significantly as it approaches the tendon. There is no abrupt transition from what is grossly determined to be muscle and tendon. This critical juncture is called the myotendinous junction (MTJ), and represents the mechanical link between the myofilaments that generate force within the muscle and the collagen fibers that transmit forces to bone. At electron microscopy, the myofibrillar membranes appear to have digit-like extensions or "folding" of the sarcolemma into which the tendon extends [2]. This folding reduces stress placed on the MTJ during loading as a result of the increased surface area [3].

Force Production and Movement

The muscle has an extensive tendinous core that permeates the whole muscle and is continuous with the perimysial connective tissue. Fibers are arranged either in parallel or oblique to the long axis of the muscle. Fibers having a parallel arrangement are referred to as fusiform. Oblique fiber arrangements are categorized as uni-, bi-, or multipennate. If the tendinous core runs along one side of the muscle with all of the fascicles approaching at an angle from one side, the muscle is referred to as pennate (feather-like). Pennation permits a larger number of fibers to be "packed" into a given cross-sectional area. This physiological cross-sectional area allows for maximal force production directed toward movement as opposed to the fiber length, which dictates the amount and speed of muscle shortening.

If the tendinous core runs centrally so that the fascicles can attach from either side within roughly the same plane, the muscle arrangement is referred to as bipennate. If the tendinous core runs centrally so that the fascicles can attach at any angle, the muscle arrangement is referred to as multipennate. Assuming that 2 muscles have a similar fiber type composition and are operating under similar contractile conditions, muscles having greater pennation consume less ATP per unit force generated than the muscles with less pennation [4]. In practical terms, this means that the cost of generating force can be reduced by recruiting muscles having greater pennation.

Once movement has been initiated, there is an ongoing process of refinement guided by muscle spindles, Golgi tendon organs, and free nerve endings collectively referred to as proprioceptors. The muscle spindle is a length-sensing mechanoreceptor capable of signaling both the rate and extent of a stretch of extrafusal fibers. Its sensitivity can be increased by input from the central nervous system. Typically found singly, muscle spindles are surrounded by the extrafusal fibers and are distributed throughout an entire muscle belly. The number of spindles present varies with the degree of control of a given muscle. For example, the muscles of the hand and neck have greater spindle density per unit muscle mass as compared to the muscles of the arms and legs.

The Golgi tendon organs are less prevalent than the muscle spindles. Their location is within the MTJ, with a ratio of 4 per 25 muscle fibers. They discharge on contraction of a muscle providing an inhibitory response to the agonist and an excitatory response to antagonists. In theory, this reflex action will allow maintenance of force developed at a joint.

Finally, free nerve endings innervate almost all structures within the muscle belly, including the extrafusal fibers, the epimysium, the larger blood vessels, and even the spindles and tendon organs. They might be sensitive to mechanical stimuli associated with muscle contraction, pressure, or stretch [5]. Still other free nerve endings respond to either temperature or chemical changes such as would occur with exercise (e.g. K^+ and lactic acid). These nerve endings may lie relatively dormant until contraction occurs, producing a local ischemic-like environment [6].

Injury and Repair

Injury

Direct trauma includes muscle contusion and laceration, and generally results in tissue hemorrhage and edema. Indirect trauma occurs secondary to exercise, stretch, and ischemia-reperfusion. Generally, the initial event in indirect trauma (particularly with exercise and overstretch of the muscle) is mechanical and occurs at the level of the contractile apparatus [7]. One hypothesis regarding the mechanism of eccentric contraction-induced injury holds that sarcomere heterogeneity increases during a stretch, so that eventually some sarcomeres are stretched beyond the length of thick and thin filament overlap. At this point, these overstretched sarcomeres are held together primarily by passive connective tissue structures and therefore rapidly undergo further elongation, which may damage the nearby sarcolemma and lead to Ca^{+2} influx.

Unregulated entry of Ca^{+2} into the cell leads to activation of Ca^{+2}-dependent proteases that cleave myofibrillar and other cytoskeletal proteins [8]. The mitochondria appear rounded and lose their regular distribution within the cell, and there is a loss of cellular glycogen. Shortly thereafter, there is disruption of desmin and sarcomeric filaments leading to Z-band streaming and A-band disruption. Collectively, these events give way to inflammatory cell invasion of the injured tissue.

Repair

The process of muscle repair begins when damaged cellular components are removed by endogenous proteases and exogenous enzymes released from infiltrating macrophages. A disruption in local blood flow may, therefore, delay repair of the damaged tissue by preventing leukocyte infiltration.

A key event in the early stages of muscle repair is invasion of both polymorphonuclear and mononucleated cells. The process is probably initiated by the release of cytokines and growth factors from injured fibers that produce chemotactic signals to surrounding inflammatory cells. The actual substances that provide this chemoattractant stimulus are unknown, although at least 4 possibilities; 1) "wound hormones" released from muscle fibers, 2) products of extracellular matrix proteolysis, 3) macrophage-derived factors, and 4) substances produced by complement system activation have been postulated [9].

At least 3 types of inflammatory cells (neutrophils, $ED1^+$ macrophages, and $ED2^+$ macrophages) may invade the injured area. The neutrophil is usually the first cell to appear following muscle injury, sometimes within the first hour [10]. A primary function of neutrophils is phagocytosis of necrotic muscle fibers and cellular debris [11]. In addition, neutrophils may serve as a source of pro-inflammatory cytokines such as IL-8 [12] and TNFα [13] that may upregulate inflammation and provide a signal for monocyte invasion of the injured tissue.

Recent observations have suggested that invading neutrophils may contribute to oxidant production following muscle stretch injury [14]. Neutrophils contain both myeloperoxidase and NADPH oxidase whose activation can lead to oxidant generation. Whether oxidants promote tissue damage or upregulate inflammation and perhaps even regeneration is yet unknown. For example, nitric oxide (NO) may be involved in satellite cell proliferation following muscle damage [15].

Monocytes also appear following injury and eventually mature and differentiate into macrophages. An early step in monocyte invasion is the migration of blood cells from the circulation to the injured area. Adhesion molecules such as E-selectin and P-selectin are critical for the influx of neutrophils and monocytes. Neutrophils are responsible for the proliferation of local macrophages, of which 2 subtypes are now recognized to play a role in muscle injury and repair. The first subpopulation expresses the $ED1^+$ antigen and is capable of invading injured muscle to phagocytose cellular debris and damaged myofibrillar material [16,17]. A second population of macrophages ($ED2^+$) reaches peak concentrations in injured muscle later than $ED1^+$ cells [18]. $ED2^+$ macrophages are resident cells present throughout the regenerative process. They do not appear to invade damaged muscle fibers, and their primary purpose may be to attract growth factors and cytokines such as IGF-1 (5), IL-6 [19], and PDGF [20] that may regulate myoblast proliferation and/or differentiation.

Cytokines are a diverse family of intercellular signaling proteins that influence the movement, proliferation, differentiation, and metabolism of target cells [21]. A variety of stimuli, including mechanical damage, oxidants, and stress hormones, may modulate or induce cytokine activity. These actions can occur by direct interaction of the cytokine with a particular receptor or by the ability of one cytokine to induce synthesis of other cytokines and hormones. At least 2 cytokines, IL-1β and TNFα, are associated with promotion of muscle inflammation. These cytokines act by induction or upregulation of various adhesion molecules [22], while cytokines such as transforming growth factor-β (TGFβ), IL-4, and IL-10 promote down regulation of the host inflammatory response. Cytokines may also be involved with satellite cell chemotaxis [23].

Myofiber Regeneration

Following the removal of damaged cellular products, both muscle fiber regeneration and new collagen synthesis occur. The mechanical and biochemical factors that control these 2 processes and their interaction are not well understood.

A host of factors exist within the injury milieu that determine both the speed and the extent of myofiber regeneration. The foundation for muscle fiber regeneration is the satellite cell, located in the periphery of the muscle fiber between the basal lamina and the sarcolemma [24]. Satellite cells are the reserve stem cell for myofiber regeneration [25–27]. With an intact basal lamina, satellite cells form myogenic cells that fuse with existing fibers or with each other to form myotubes. In vitro experiments have demonstrated satellite cell proliferation early in the post-injury period [26]. Interestingly, the sarcolemma can exert a negative control on satellite cell proliferation and differentiation [27]. Furthermore, mechanical events can also affect the rate of myofiber regeneration [27].

The postinjury response of the satellite cell appears similar to the process of fetal muscle development.

Expression of myosin heavy chain isoforms provides a useful marker of differentiation in the post-injury period [26]. The time from injury to initiation of satellite cell proliferation is affected by several factors including species, type of injury, and metabolic state of the muscle [28]. Although the recruitment of satellite cells appears to be limited between muscles, there is apparently free and unimpeded recruitment of these cells along the entire length of the fiber [5]. Growth factors stimulate and inhibit satellite cell proliferation and differentiation. The majority of attention has been directed toward basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF-I), and transforming growth factor (TGF-β) [28,29]. These growth factors are made available to the injured tissue through disruption of the extracellular matrix, local synthesis and secretion, and blood-borne arrival. Receptors for these growth factors are located on the surface of satellite cells and terminally differentiating myoblasts. IGF-1, under the control of growth hormone, is expressed in increased amounts during growth and repair [29,30]. Skeletal muscle regeneration results in an increased expression of IGF-1 in satellite cells, myoblasts, and myotubes [30]. An acute bout of eccentric exercise increases IGF-1 levels in muscle tissue for up to 4 days [29]. Taken together, these findings suggest that myoblasts and satellite cells may discriminate between different stimuli to produce cytokines that may influence and promote the body's immunological response to muscle injury.

Collagen Synthesis

Successful repair of damaged muscle is a delicate balance between myofiber regeneration and collagen synthesis. Clearly, some connective tissue synthesis is necessary for proper transfer of forces across the myotendinous junction and for adequate muscle tensile strength. On the other hand, excessive production of connective tissue can lead to scarring and fibrosis.

Four main collagen forms, I, III, IV, and V, are present in skeletal muscle [31], with some recent evidence for gene expression of smaller amounts of other types [32]. Fibroblasts produce IL-6 [9] and IL-1α [33], which can help to sustain the inflammatory response. Pro-inflammatory cytokines such as IL-1 and TNF also stimulate fibroblasts to proliferate and synthesize collagen [33,34]. Type I, the major fibrillar collagen, is present primarily in the muscle's epimysium and perimysium. This collagen possesses relatively high tensile strength and stiffness, and is therefore most suitable for transmission of muscle-tendon forces. Type III collagen, the other major fibrillar collagen, is located mainly in the perimysium and the endomysium, and forms thinner, more elastic fibers. Following injury to skeletal muscle, both Type I and III collagen are synthesized. Type III collagen synthesis increases even before mature fibroblasts can be detected, with primitive, multipotent cells the presumed source. During the later events of repair, there is marked production of Type I collagen and restoration of the normal I : III ratio [35]. Several studies illustrate the presence of a high proportion of Type III collagen, in some cases for up to 6 weeks following injury [35,36]. In addition to Type I and III collagen, immunological studies have suggested that Type V collagen production occurs with myofiber regeneration [31,37]. A few studies have also shown Type IV collagen within the healing matrix following muscle trauma [35,36].

Conditions of Abnormal Repair

Excessive collagen synthesis and subsequent scar formation can inhibit myofiber regeneration [35,36,38,39]. A recent study of stretch injury suggests that the molecular expression of mRNA for Type III collagen is increased very early in the post-injury period. Perhaps more importantly, there was a 2-fold increase in Type III collagen expression compared with myosin and this difference persisted for at least 5 days [32]. Therefore, for yet to be determined reasons, the early events of injury and repair favor new collagen synthesis rather than myofiber regeneration.

A second condition of abnormal repair that can occur following direct muscle trauma is myositis ossificans. A major risk factor for development of traumatic myositis is re-injury early in the recovery period [40]. Myositis ossificans can occur when severe soft tissue compression against underlying bone results in muscle fiber disruption along with capillary and vascular injury resulting in significant bleeding and edema. A palpable mass may be noted and radiographically evident 2 to 4 weeks following the injury. Eventually, heterotopic bone can form in the muscle, and can be contiguous with normal bone, periosteum, or completely free of any connection with existing bone. There appear to be differences amongst species that dictate the location of heterotopic bone formation.

Stretch Injury to the Musculotendinous Junction

Muscle Stretch Injury

Stretch-induced injuries occur frequently in high velocity sports e.g. sprinting, jumping and in the workplace, where sudden change of direction can lead to overload of the muscle-tendon unit. Although animal studies have shown that the site of injury can vary with velocity of stretch [41], clinical studies with MRI have usually localized the injury to the MTJ [42]. The exact reason why these injuries occur so frequently at the MTJ is unclear, and probably involves a number of factors. Most importantly,

perhaps, is the difference in muscle and tendon stiffness locally at the MTJ. Muscles most at risk for stretch injury are the 2-joint or bi-articular muscles such as the hamstrings and quadriceps. In general, the primary function of these muscle groups is limb deceleration during body locomotion. This observation suggests the importance of muscles as energy absorbers and rehabilitation programs should be directed specifically at this important function.

In a response to a muscle stretch injury, individuals will often experience local tenderness at the site of injury along with pain and stiffness. Blood can collect within the subcutaneous tissue, and ecchymosis often results within a few days. In contrast to contusion injury, bleeding is not confined to the body of the muscle proper, and MRI studies have confirmed the perifascial localization of fluid [18,42].

There is no consensus for the management of muscle stretch injury. Immediate management usually involves relative rest, ice, and compression of the affected muscle, although pain may be the major guiding factor in the early post-injury period. Immobilization should probably be avoided if pain is tolerable [36]. The efficacy of medications such as non-steroidal anti-inflammatories (NSAIDs) is not well defined, and some preliminary evidence suggests that NSAIDs may delay myofiber regeneration [43,44]. Other authors have advocated the use of intramuscular corticosteroid injections, though the level of epidemiological evidence to support this course of management is questionable [45]. Surgical intervention has been advocated at times, although indications are not clear. Ice probably helps to limit swelling, although the basic science to support this strategy is lacking. There is a need for well-controlled, systematic laboratory and clinical studies to determine optimal treatment and rehabilitation strategies. Isokinetic strengthening is probably preferred to isometric activities, as the resistance is accommodating and the injured individual can work at a comfortable level through a full range of motion. Furthermore, objective validated criteria for safe return to competition are not currently available. At present, the general management consensus includes: 1) begin active stretching and muscle activation as soon as tolerated making certain to avoid large forces initially; 2) use a gradual increase in strength intensity during rehabilitation course, strength in injured area should equal that of its contralateral side prior to release to competition; and 3) strive for complete recovery of muscle length and joint range of motion prior to release to uncontrolled sport activity although resuming practice can be allowed with mild discomfort.

Delayed Onset Muscle Soreness (DOMS)

It is not clear whether DOMS represents injury or simply a phenomenon characterized as "muscle damage." DOMS may perhaps be more accurately categorized as a natural result of eccentric activity that is much too intense or simply unfamiliar to the individual. DOMS is characterized as muscular pain that is not felt for at least 12 hours after the completion of activity. An individual can present with diffuse tenderness to palpation, muscle weakness, and restricted range of motion. The soreness is different from the transient discomfort associated with heavy physical training, and there is typically evidence of measurable tissue damage including disruption of the muscle fiber contractile elements, abnormal mitochondria and loss of muscle membrane integrity [46,47]. Creatine kinase and myoglobin levels are elevated and serve as indirect indicators of muscle damage [48]. The recovery time course is relatively predictable. Therefore, DOMS may be a favorable adaptation associated with recovery that delivers a preventive measure from future injury.

Some athletes consider DOMS nothing more than a nuisance, and will continue their normal training pattern. Currently, research remains inconclusive about the validity of using DOMS as an indicator for significantly modifying a training program.

Physical Training and Injury Prevention

Strength Training

Strength training produces numerous adaptive benefits on muscle, tendon, ligament, and bone [49]. These adaptations help to justify the implementation of elaborate sports conditioning programs. However, little information exists with regard to the specific role of strength training in MTJ injury prevention.

As mentioned previously, muscle is highly adaptable. In both the training and rehabilitation settings, either muscle hypertrophy or the absolute amount of weight one can lift have been used as markers of training success. However, neither impart adequate protection against injury if a movement is executed improperly or too slowly to achieve the required power output. Furthermore, if the strength of a muscle group is developed disproportionately relative to its antagonist, or its contralateral side, an athlete could be at risk for an injury. For example, a hamstring strength of less than 60% of the quadriceps may place an athlete at risk for a muscle strain injury [50].

As with all forms of training, a paradox exists between the risk and reward associated with strength training. It is a challenge to determine exactly how much of a stimulus is required for the program to be effective; it is presumed that the reward is improved sport performance with little or no time lost due to injury. However, research does not conclusively support this theory. A search of MedLine (1966 to Dec 2000) and SportDiscus (1949 to Dec 2000) yielded 25 articles using the key words

"strength training" and "injury prevention." Of these, 12 were research papers published in peer-reviewed journals with the remainder being "how-to" information for the practitioner. When searching with the key word "eccentrics," 10 peer-reviewed articles were referenced. However, these articles address DOMS and not primary or secondary MTJ injury prevention. Although eccentric muscle contractions are largely responsible for inducing muscle damage, there is also evidence suggesting of a protective effect when eccentric exercise is performed isokinetically. However, not all studies have shown such a protective effect using isokinetic eccentric training.

Flexibility Training

In practice, it is customary for an athlete to perform a pre-exercise warmup followed by static stretching. This has been assumed for years as the optimal training method for injury prevention, but there is little scientific evidence supporting this practice [51–53]. In fact, a typical stretching protocol performed during a pre-training warm-up did not have an impact on the incidence of exercise related injuries in army recruits [54].

The presumed goal of stretching is to improve the functional range-of-motion (ROM) of a given joint or series of joints. Stretching is purported to lengthen the MTJ, thereby gaining length in movement. Clearly, optimum ROM for any given individual is specific to the demands of their particular sport. This is obvious when comparing the ROM demands of a gymnast or martial artist versus that of a baseball player or soccer player. The major biological consideration that affects joint ROM is the collagenous tissue, and includes tendons, ligaments, joint capsules, aponeuroses, and fascial sheaths as well as the latticework of muscle itself.

Empirically, it is believed that flexibility training will, with time and diligence, improve joint ROM. What is not well understood is how to appropriately quantify ROM in a meaningful way or how to prescribe a proper stretching program. Factors affecting measurements include age, gender, body type, one's ability to relax, type and intensity of activity as well as the affect of other activities outside of the competitive sport. Making recommendations based upon a measure or series of measures can often be speculative at best and, if used, must be balanced by the observations seen in the competitive arena. Stretching is most often prescribed in a static state with little or no change in joint angle. However, ballistic stretching and proprioceptive neuromuscular facilitation are also used with the former having been defined as "dangerous" and the latter as beneficial for joint ROM. Much work needs to be done to determine the proper dose response for MTJ injury prevention.

Conclusion

Skeletal muscle, and in particular the MTJ, are organized and structurally complex units that function primarily for joint rotation, motion and energy absorption. Injury to the myotendinous junction typically results from a combination of muscle stimulation and stretch. Successful repair of damaged tissue includes a series of events initiated by cellular infiltration and inflammation. Events in DOMS and acute inflammation are similar, and include pain, swelling, and loss of function; evidence of macrophage infiltrates; increased lysosomal activity and increased circulating levels of some of the acute phase proteins; and histological changes during the initial 72 hours [55].

A group of cytokines and growth factors yet to be completed identified help to orchestrate successful repair. Conditions not yet well understood appear to favor new collagen synthesis rather than myofiber regeneration supporting the basis for scar formation. Consensus on optimal treatment and rehabilitation strategies for stretch injury to skeletal muscle remain a topic of debate.

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9
Insertional Tendinopathy in Sports

Per Renström and Thomas Hach

Insertional tendinopathies are common. They are still very much debated, as their management is still not optimal and is time consuming. The clinical picture arises from degenerative disorders at the osteotendinous junction. The diagnosis can be straightforward, but a wide variety of differential diagnoses must be considered. Management is based on a progressive controlled exercise program, which is the key to stimulate a biological healing response. The main part of this training program includes eccentric training and stretching. Initially, the program should be supervised, as it is difficult to dose correctly. Orthotic devices have clinically some good effect. Among modalities, acupuncture has recently been used. Some authors report good results with extracorporeal shock-wave therapy, but the scientific evidence is still under scrutiny. Cortisone injections are the last line of treatment, and their effect is usually short lived. These injections should therefore be combined with some rest and gradually increased exercises. Surgery may be indicated in 5% to 10% of cases and consists of excision of the affected tissue, with a success rate of 60% to 80%. Insertional tendinopathies still continue to be an enigma and may even develop to be a nemesis for both athletes and physicians.

Treatment of tendon disorders has made great advances in the past few years, but there still is confusing terminology concerning tendon injuries. The occurrence of tendinitis is rare, and tendinosis should remain a histological diagnosis. Accordingly, we refer to problems of the tendon insertion in general as insertional tendinopathies. The term enthesiopathy is a synonym usually reserved for rheumatological descriptions. The tendon insertion into bone—the osteotendinous junction (OTJ)—has not been widely studied. This chapter reviews basic science, anatomy, and pathophysiology of tendon insertion to provide the fundamentals to understand the clinical manifestations of insertional tendinopathies. Furthermore, we give some details on the issues of tendon healing and rehabilitation.

Insertional tendinopathies are defined as one form of tendon overuse injury characterized by pain and discomfort at and around the OTJ [31]. Insertional tendinopathies represent 15% to 25% of all tendinopathies [31,41,62], and long-term results after both conventional and surgical treatment are not as satisfactory as for other tendon disorders [31,62]. The most common anatomic sites of insertional tendinopathies are the rotator cuff, the lateral epicondyle of the humerus, the lower pole of the patella, and the Achilles tendon insertion. Since these are the most common sites of lesions [31,41,92], and histopathological studies mainly refer to these 4 areas, the section on insertional disorders in general is followed by clinical examples at these 4 areas.

Anatomy

The tendon insertion into bone is a complex anatomical structure, where collagen fibrils from the tendon insert into bone matrix, i.e. viscoelastic tendon tissue is connected to rigid lamellar bone. There are 2 forms of OTJs: fibrous and fibrocartilaginous [11,12], or indirect and direct insertions [111]. Fibrous tendon insertions are typical of tendons that attach to the periosteum of long bones, whereas fibrocartilaginous insertions are typical of tendons that attach to epiphyses [7,8,25,111]. Since fibrous tendon insertions are less common and rarely involved in specific pathological conditions, we shall focus on fibrocartilaginous tendon insertions. Notably, the gradual change from tendon proper to bone tissue occurs within 1 mm [68].

The first scientific description of tendon insertions dates back to 1929 [22]. The author divided the OTJ into 4 zones: tendon, fibrocartilage, calcified fibrocartilage, and bone [12]. This concept is still valid [7,20,31,62,96].

Tendon Zone

The tendon zone of the OTJ consists of dense collagen bundles, extracellular matrix—predominantly chondroitin sulfate, dermatan sulfate and hyaluronic acid [45,68]—and interspersed elongated tenocytes with ellipsoid nuclei [31,33].

Various different types of collagen are present in tendon tissue: Collagen Type I is the main constituent of the tendon zone. Closer to the zone of fibrocartilage, the amount of collagen Type II continuously increases. Collagen Type III can also be found in tendons, especially during the process of tendon healing [31,62]. In addition, the cartilaginous parts contain collagen Types IX, X, and XI, whereas collagen Type IV is found in the basement membrane. Collagen, the body's strongest protein, consists of tropocollagen microfibrils building the smallest structural units of tendons. These soluble proteins are right-handed triple helixes 280 nm long and 1.5 nm wide, formed by 3 left-handed polypeptide chains. Five tropocollagen microfibrils combine to form insoluble collagen fibrils of 20 to 150 nm in diameter.

This process is supported by the formation of covalent collagen crosslinks. Intermicrofibrillary crosslinks provide collagen fibers with tensile strength and low compliance. Crosslinks can be reducible and nonreducible. Moreover, a balance of hydroxylysino-5-keto-norleucin and dehydroxy-hydroxylysino-norleucin crosslinks exists. A change in the crosslinking pattern with age is supposed to account for increased mechanical stiffness and decreased tensile strength values [106]. Collagen fibrils are collected into fibers, which form fiber bundles and finally create the tendon itself [31,32,45,92].

Consequently, the tensile strength of tendons relies on collagen, whereas noncollagenous matrix proteins provide structural support and mediate cell-matrix interactions. Furthermore, tenascin-C and fibronectin play a major role in binding tendinous collagen together [9,35].

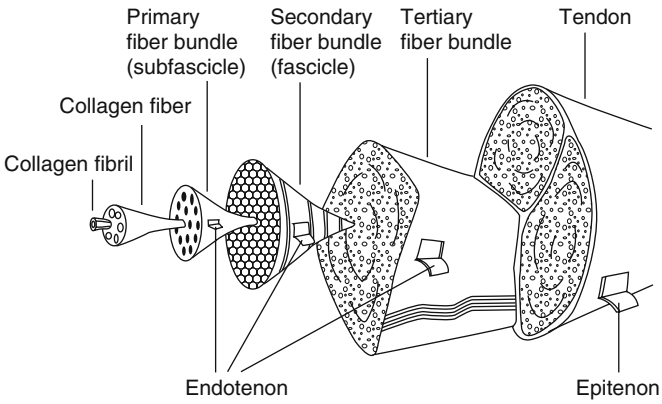

FIGURE 9-1. Organization of tendon structure.

Tendon cells adopt an elaborate shape to maintain continuous cell contact via gap junctions. Therefore, the relatively few interspersed cells are functionally interrelated, and can sense changes in mechanical load. In this fashion, the extracellular matrix can be modified [12] (see Figure 9-1).

Fibrocartilage Zone

The fibrocartilage zone of the OTJ shows a gradual tissue change along the collagen fibers (see Figure 9-2). Embryological studies explain the epiphyseal origin of tendon and fibrocartilage in OTJs. The gradation of cell phenotype between uncalcified fibrocartilage and dense fibrous tissue seems a logical consequence, taking into account that fibrocartilage cells develop from tenocytes by metaplasia [12]. In contrast to tenocytes, fibrocartilage cells are usually round or oval. They also lack gap junctions, so that fibrocartilage cells act as a barrier to communication between osteocytes and tenocytes. In addition, there is also a vascular barrier, as noncalcified fibrocartilage lacks blood vessels.

The fibrocartilage at this location may have the following functions:

- Two-layered defense system against excessive shear stress [96]
- *Dehnungsbremse* (stretching brake) [46].
- Device reducing wear and tear at insertion sites [11].
- Tendon protection of mechanical functional significance [9].

Collagen fibers pass directly through the zone of fibrocartilage stabilized by the extracellular matrix. Tenascin-C content is high in the fibrocartilage layer of the OTJ, reflecting good adhesive function when high forces are transmitted [31,34,35].

Calcified Fibrocartilage Zone

The calcified fibrocartilage zone of the OTJ is on average 100 to 300 µm wide, but varies depending on anatomical site, tensile forces, and exercise [11,31,46,62]. It is delineated by a basophilic line (tidemark, blue line, or cement line) clearly visible but not always continuous under a light microscope [20,31,32]. Scanning electron microscopy does not show a significant tidemark. Collagen fibers within the calcified fibrocartilage are not crimped passing through calcified fibrocartilaginous tissue [20].

Bone Zone

Bone at the OTJs has the least tensile strength of this complex. Collagen fibers enter the bone matrix directly without merging to bony lamellae. The mechanism of

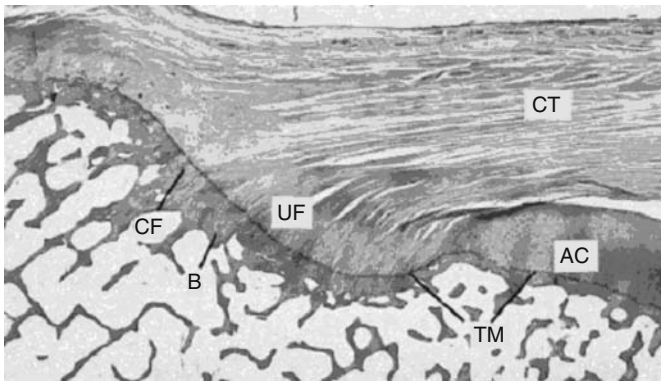

Figure 9-2. Osteotendinous junction. The 4 zones of tissue at the tendon insertion to bone: Dense fibrous connective tissue (CT), uncalcified fibrocartilage (UF), calcified fibrocartilage (CF), and bone (B). The calcified and uncalcified fibrocartilage are separated by a tidemark (TM) that is straight and continuous with a similar tidemark in the adjacent articular cartilage (AC).

adhesion is not yet fully understood. Also, the development of bone at the OTJs is from different origin than other bone structures: possibly, the bony insertion develops from tendon fibrocartilage [20,70].

Blood Supply

Tendons have a poor blood supply. The blood flow of tendons is only about one-third of the blood flow of muscle [11]. In tendon regions where hypovascularity is associated with friction, torsion, or compression, there seems to be an increased risk for tearing, calcification, and degenerative changes [31,41,54,84,108]. Blood supply reaches the OTJ from paratenon and periosteum. Approximately the lower third of a tendon is perfused in this fashion. There is clear distinction between vessels in calcified and noncalcified fibrocartilage, because the calcification of fibrocartilage acts as an impenetrable border for anastomoses, and fibrocartilage itself is almost completely avascular [11,31–33,41,46,62]. Blood supply to the OTJ increases during exercise and healing [36,47]. Histopathological findings suggest a vascular proliferation in tendinosis [31,33,41,47,63,72].

Nerve Supply

Nerve supply to the OTJ is mainly afferent. Most nerve endings in tendons are found at the myotendinous junction. Free nerve endings near the OTJ act as pain receptors, and are predominantly found in the connective tissue of the attachment site [22,31,46,62]. Localized pain at the OTJ is mediated by free nerve endings. Nerve fibers accompanying small blood vessels have an important role in tissue vasoregulation. Various neuropeptides amplify neural activity on blood vessels and tenocytes, and may have a role in tendon healing [1].

Juxta Insertion Site

The juxta insertion site is specific for every tendon. Often adjacent bursae and paratenon tissue are also affected by degenerative processes or associated inflammation. At many tendon attachment sites, the juxta insertion structures act as protective devices for the OTJs. Small synovial bursae allow the tendon to move freely relative to the bone. Periosteal cartilage on the bone protects tendons from friction. Examples of juxta insertion disorders are paratendinopathy, retrocalcaneal bursitis, and infrapatellar bursitis [41,46].

Summary

Overall, the OTJ is a durable bond between tendon and bone. Because of its complex and differentiated structure (Table 9-1), it provides protection for the insertion site and functionality of the muscle attachment [9,11,62,84]. Tendon ruptures usually do not involve the OTJ [20,28]. However, when degenerated, OTJs are the weakest link of the musculotendinous unit [94]. Hypovascularity can act as a contributing factor to insertional tendinopathies [4,31,37,42]. Furthermore, minimal pliability, a perpendicular architectural arrangement against the direction of muscle force, and a relatively small insertion zone compared to muscle size supposedly predispose the OTJ to injury [73].

General Aspects of Insertional Tendinopathies

Functional and structural disorders of the OTJ can be due to rheumatological disorders, sports activities, or degenerative changes [52].

Rheumatological conditions such as rheumatoid arthritis, spondylarthropathy, calcium pyrophosphate deposition, and diffuse skeletal hyperostosis play a major role concerning insertional tendinopathies [99]. Since enthesopathies—in rheumatological terms—belong to a different clinical entity, they are not discussed here. During the diagnostic workup, a rheumatological contribution to insertional tendinopathies must not be overlooked [102]. Insertional tendinopathies can manifest at the insertion of every tendon of the human body. The most common anatomic sites are rotator cuff, lateral humeral epicondyle, patella, and Achilles tendon. Insertional tendinopathies in the groin are also not uncommon, and are most difficult problems [83]. The tendons of the foot, wrist, and fingers can also be affected [31].

Table 9-1. Characteristics of the different zones of the OTJ

	Collagen type	Vascularity	Nerve supply	Cellularity	Strain
Tendon	I	+	++	+	+++
Fibrocartilage	II	–	+	+	++
Calcified fibrocartilage	II	–	+	+	+
Bone	I	+++	+++	++	+

Sports activities and degenerative changes are closely interwoven reasons for insertional tendinopathies. In athletes, overuse-related microtrauma can induce premature tendinosis, and aggravate degenerative changes. Overuse injuries account for 30% to 50% of all sports injuries. Tendon overuse injuries in particular are the most common reason for breaks in training and competition [38]. Insertional tendinopathies account for 15% to 25% of sports-related tendon disorders. The etiology of insertional tendinopathies still needs further elucidation. Overuse is a well-established etiologic factor for these injuries [31,33,38,41]. To effectively prevent insertional tendinopathies, it is important to understand, identify, and affect predisposing risk factors. Intrinsic and extrinsic risk factors can be differentiated. The most important intrinsic risk factors are: malalignments, decreased flexibility, muscle weakness and imbalance, overweight, and predisposing conditions, such as inflammatory arthritides, Haglund deformity, etc. Crucial extrinsic—and consequently more easily affectable—risk factors are: excessive load, training errors, and poor equipment [31,92]. Predisposing risk factors will be discussed in the treatment section.

Pathogenesis

An overuse injury is defined as a recurring orthopedic problem and pain in the musculoskeletal system, which begins during exertion because of repetitive microtrauma [31]. The OTJ adapts to increasing mechanical demands by changes in collagen cross-sectional area [36], extracellular matrix [34,35], and fibrocartilage distribution [10] within physiological limits. When repair and adaptation capabilities are exceeded, degenerative changes result (Figure 9-3). At histopathology, a dull, gray, and friable appearance is typical of the degenerative process in contrast to a shiny, white, and firm normal tendon [31,47,63]. Microscopically, the specimens show thinning, disruption of collagen fibers, increased vascularity and cellularity, tenocyte dedifferentiation/alteration (rounded nuclei and blastlike morphology), granulation tissue, increased ground substance, fibrocartilaginous metaplasia, and microtears. Inflammatory cells are not normally seen in insertional tendinopathies [4,31,33,41,55,89,93]. Repeated tendon strains to 4% to 8% of original length cause microscopic tendon fiber rupture. These repetitive microtraumata lead to overuse injury [31]. Partial or complete tendon ruptures result from strains of greater than 8% of original length.

Recently, investigations on the strain patterns of the patellar tendon suggested that stress shielding rather than excessive tensile loads may be a causative factor in patellar tendinopathy [123]. This goes hand in hand with the description of compressive loads causing degenerative changes in tendons and tendon insertions respectively [124–126]. These findings warrant further investigation of biomechanical aspects in insertional

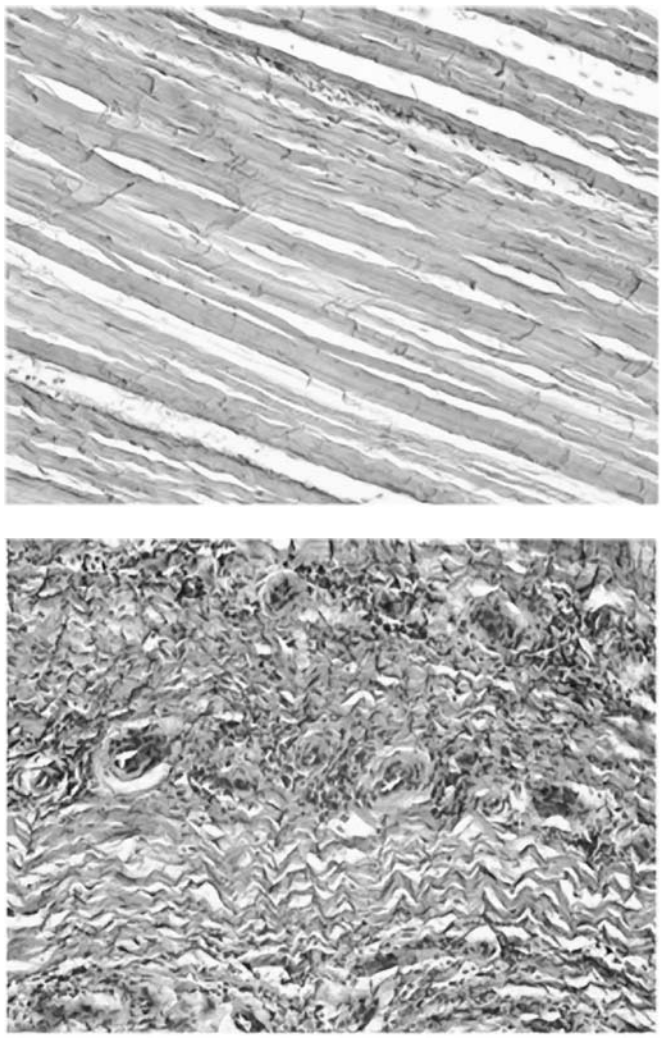

Figure 9-3. (A) Normal tendon. Photomicrograph showing parallel collagen fiber distribution and uniform-appearing collagen structure oriented along the axis of the tendon (Hematoxylin/Eosin). (B) Tendinosis. Photomicrograph showing hypercellularity, wavy collagen structure, and hypervascularity (Hematoxylin/Eosin).

tendinopathies, especially for athletes and rehabilitative exercises.

Insufficient blood supply is also regarded as a pathogenetic factor contributing to tendon failure, insertional disorders and overuse injury in general, respectively [31,37]. The vascular elements of a tendon can also be damaged by microtrauma. Therefore, degenerative processes are perpetuated. Finally, both overuse injury and impaired circulation interfere with collagen crosslinking patterns. As a consequence, the above mentioned pathology develops, and microtears expand in the tendon and the fibrocartilage zone of the OTJ [31]. The tendon insertion is thus weakened, eventually leading to microtears and the clinical findings of pain, crepitus, and tenderness.

Insertional tendinopathies are degenerative disorders that do not arise from chronic inflammation. Although misnomers such as lateral epicondylitis and chronic patellar tendinitis persist, inflammatory processes are rarely involved in insertional disorders [6,31,33,40–42,55,89, 110]. Sometimes associated structures can become inflamed (paratenonitis, bursitis, etc.), but tendon insertion tissue damage is caused by exceeded repair capabilities. A tendon probably never reaches its original strength after healing [31,42], and for this reason tendon healing probably cannot be considered to confer *restitutio ad integrum*.

Diagnosis

A detailed history is essential. As tendinosis per se can be asymptomatic, clinical history related to sports activities or manual work can provide valuable information. Insidious onset of symptoms is characteristic of degenerative disorders. If certain activities or movements are associated with pain, the location of the lesion can be pinpointed.

The classic orthopedic examination scheme of "look, feel, and move" is undertaken. Inspection may reveal muscle atrophy, compensatory postures, and swelling because of associated bursitis or paratenonitis.

Palpation may detect definite points of tenderness (typical for insertional tendinopathies), bony prominences (e.g. Haglund deformity), crepitus (e.g. Achilles paratenonitis or calcific tendinopathy), and nodules or gaps in the tendon [31,92].

Active and passive motion usually show characteristic deficits corresponding to the affected tendons. Early after the onset of symptoms, the range of motion is frequently unaffected, but it decreases during the course of deterioration.

Diagnostic studies of insertional tendinopathies include plain radiography, ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), and bone scanning. Bony abnormalities can be detected and fractures can be ruled out using routine and soft tissue radiographs. Tendon avulsions or bone fragments at the insertion (e.g. Osgood-Schlatter disease) can also be easily detected on plain radiographs [31,92]. Special radiographic views can facilitate the diagnosis of insertional tendinopathies at certain anatomic sites, e.g. shoulder, knee, etc.

Diagnostic ultrasonography is a quick, safe, noninvasive, easily obtainable, and inexpensive method of tendon evaluation. In Europe, it is much more commonly used than in North America. Since the possible shortcomings of diagnostic ultrasonography, such as limited field of view, limited soft tissue contrast, and reduced sensitivity are continuously improved upon, its reliability and field of application are continuously enhanced. Apart from that, operator dependency is an important feature of diagnostic ultrasonography that warrants educational and training programs for soft tissue evaluation. In the field of tendon disorders, diagnostic ultrasonography is particularly useful for the detection of tears at the tendon insertion or attachment, and associated degenerative or inflammatory changes [5,31,56,92]. Furthermore, diagnostic ultrasonography is a practical method for follow-up examinations [43].

MRI is considered by some as the standard for soft tissue imaging [105] and visualization of tendon pathology [92]. High intrinsic tissue contrast and high spatial resolution are the striking features that allow detailed analysis of tendon pathology [81]. Since MRI offers excellent diagnostic results, but is expensive, it should be confined to evaluations when *only* MRI results can propose therapeutic consequences [92]. The possibility of detecting even slight pathological changes by MRI [81] allows the identification of the early stages of insertional pathology, so that successful secondary preventive measures can be implemented.

CT has limited value in tendon pathology, since its limited contrast makes differentiation of normal and pathological conditions difficult [81]. In principle, it is a useful aid, and insertional disorders, if they involve the bone, can be detected [31]. Nevertheless, a CT scan is rarely indicated in insertional tendinopathy.

Bone scanning is a sensitive method for assessing pathologic activity in insertional tendinopathies. Since its specificity is low, and the soft tissues are not demonstrated [31], bone scanning should be limited to evaluations of insertional tendinopathies associated with other diseases that cause bone alterations, e.g. rheumatoid arthritis, spondylarthropathies, osteoporosis, etc.

Management

Even though the outcomes of nonoperative and operative management are improving, the methods are still

mostly empirically based and often lack scientific evidence [31,92]. When it comes to establishing a management plan for insertional tendinopathies, the patient's state of health must be identified, and management goals should be discussed. The management principles for acute and chronic insertional tendon injuries are outlined hereinafter.

Acute insertional tendinopathies are rare. Often, associated inflammation causes acute pain. In case of acute symptoms, e.g. avulsions, partial or full-thickness tears, bursitis, or paratenonitis, the management follows the well-known rules of managing acute sports injuries. Protection, rest, ice, compression, elevation, support (PRICES), and NSAIDs are widely used [31,59]. Avulsions should be repaired surgically, and surgery for tendon tears must be considered on the basis of anatomical site, loss of function, and goals of rehabilitation. Both operative and nonoperative approaches produce a high percentage of good results [31,42,54,92,99].

Chronic insertional tendinopathies are often recalcitrant to conservative management [44,92]. The ultimate goal of any form of management is to restore the integrity of the tendon-bone unit. Therefore, further injury must be avoided, and the healing process must be supported. In addition, symptomatic management can be added. Nonoperative methods are the primary methods of choice. Operative management should be limited to patients who have failed conservative management for at least 6 to 9 months, or are restricted in their daily life activities. Correction of predisposing risk factors, functional rest, stretching, strengthening, and physical therapy are important management methods. Recently, extracorporeal shock-wave therapy (ESWT) has been used on tennis elbow, Achilles tendinopathy, and tendinoses associated with tendon calcification. Preliminary results are promising, but some studies also show inconsistent results [13,29,88].

Correction of Predisposing Risk Factors

- Excessive load on the body
  Repeated overload is the main risk factor for insertional tendinopathies in athletes and manual workers [19,31,33,44,82]. Counter-force braces for jumper's knee and tennis elbow are the most popular management options, acting directly on muscle force to the tendon insertion. They constitute an additional option of nonoperative management.

  The following extrinsic and intrinsic factors contribute to and aggravate the problem.
- Training errors
  Training errors are considered the most important extrinsic risk factor for overuse sports injuries, and probably contribute to 60% to 80% of tendon and other overuse injuries [31,92], especially in runners. In general, the most important training errors are too long distance, too high intensity, and too fast progression. Therefore, failure to allow for physical adaptation results in degenerative changes. Excessive, monotonous, asymmetric training, sudden changes in training program or training ground, insufficient warm-up, inadequate general conditioning, as well as poor technique and fatigue training all jeopardize the athlete's tendons. Evaluation and modification of the training program and correction of poor technique, e.g. faulty backhand technique in tennis elbow, or modified landing in basketball or volleyball in jumper's knee may markedly improve if not resolve the patient's symptoms [31,42,92].
- Poor equipment
  Poor equipment is also a major risk factor. Running shoes are important to stabilize the foot and reduce impact forces. The replacement of unfitted or worn-out shoes with appropriate ones is a valuable first step in successful management. Tennis racquets that are too stiff or strung too tightly may initiate symptoms of tennis elbow. Hand paddles in swimming may induce rotator cuff tendinopathy. Inadequate adjustment of bicycle seats can lead to problems of the knee extensor apparatus [31]. Once identified, these conditions can be tackled more easily.
- Malalignments
  Malalignments are a serious intrinsic predisposing risk factor for insertional tendinopathies. Hyperpronation of the foot is both the most common and best described malalignment that can result in Achilles tendon insertion disorders, patellofemoral stress syndrome, runner's knee, etc. A high-riding patella and patellar hypermobility are associated with jumper's knee, even though the cause-and-effect relationship is unclear [23,27,31,42,79,87]. As the correction of malalignments can be simple, they must not be overlooked.
- Decreased flexibility—Muscle weakness and imbalance
  Low flexibility and interference of muscle function predispose to and perpetuate chronic tendon disorders. Especially for insertional tendinopathies, optimal muscle and tendon function is essential. Stretching and strengthening are a mainstay of management and prevention.
- Overweight
  The detrimental effects of overweight on the musculoskeletal system are well known, recognized, and scientifically proven. Sedentary lifestyle is associated with degenerative tendon disorders [31,33,37,41,106]. Moreover, overweight, sedentary lifestyle and inactivity impair adaptive capabilities and the healing process of tendons.

Functional Rest

As in the acute phase, rest and immobilization are also commonly prescribed to relieve pain in chronic degenerative tendon disorders. Initially, rest protects from further injury and allows the patient to better tolerate a physical therapy program [92]. Since pain at the insertion site is very common and may persist over a longer period of time [25,62], protracted immobilization should be avoided to prevent its adverse effects [31,92]. Therefore, early mobilization should be implemented. The term "functional rest" emphasizes treating the injured body parts with care while still maintaining general body conditioning.

Stretching

Stretching is considered an important element of an integrated management protocol for tendon injuries [23,83,98,110]. As the musculotendinous units in insertional tendinopathies are frequently tight due to disuse or protective muscle contraction, stretching is advisable to restore function by stress relaxation and reduction of stiffness [92]. Furthermore, mechanical stimulation leads to adaptive changes in the tendon [11,35,106]. Therefore, controlled stretching is likely to result in acceleration of collagen synthesis, fibril neoformation, and proper fiber alignment, and thus increase the tensile strength of the tendon [36]. The recommended stretching technique is contract, relax, antagonist contract (CRAC). Jerky motion, rapid movements, and ballistic stretching should be avoided during rehabilitation. Stretching can be used for both management and prevention of insertional tendinopathies [92].

Strengthening

Strengthening of the affected muscle-tendon unit is another mainstay of nonoperative management of insertional tendinopathies. The strengthening program should begin as soon as possible after the diagnosis or after the acute associated inflammation phase. The primary goal is to restore complete function of the damaged tissue. Pain is a useful guide for progression in a strengthening program. Exercises should be carried out until the patients feels pain, and possibly slightly beyond that limit [75,92]. Further strain will result in recurrent microtrauma, and should be avoided. In this way, strengthening can progress from light resistance exercises to eccentric exercises. Maximum stress is placed upon a tendon during eccentric exercises, and only if one can strengthen the tendon to withstand these stresses will the tendon be able to cope and be protected against reinjury [24]. Since mechanical loading and adaptive processes are closely interrelated [34,35], the aim of maximal load without microtraumatization is appropriate. The eccentric strengthening program should consist of warm-up and stretching, eccentric exercises, postexercise stretching, and icing or cold in case of swelling or pain [24,31,92]. Finally, it is important to evaluate and encourage the patient's improvements in strength and flexibility. Traditionally, return to limited sports activity is possible with full range of movement and 80% to 90% of the strength of the uninjured extremity, which can be objectively measured by functional testing [67]. Before returning to full activity, sports-specific activities must be tested. In this way, premature return to sports, a common cause for the recurrence of symptoms, can be avoided.

Physical Therapy

Physical therapy is frequently employed together with stretching and strengthening. Heat, cold, therapeutic ultrasound, and electrical stimulation are the physical therapy modalities most commonly used. There is still little scientific evidence on the effectiveness of physical therapy, but patients generally describe physical therapy as comfortable and helpful. It can be generally recommended to use heat to prepare for stretching and strengthening exercises and cold to support the alleviation after strenuous exercise. A more detailed description of the effects of physical therapy is given in Figure 9-4.

Extracorporeal shock-wave therapy (ESWT) may be effective in some patients not responding to nonoperative management. The success rates for management of insertional tendinopathies such as tennis elbow, Achilles insertion disorders, and shoulder tendinoses are estimated at 50% to 80% [29,88]. Since the prognosis for recalcitrant tendinopathies is good, and ESWT does not show major adverse effects, it is an option before surgery is planned. However, the excellent results reported in

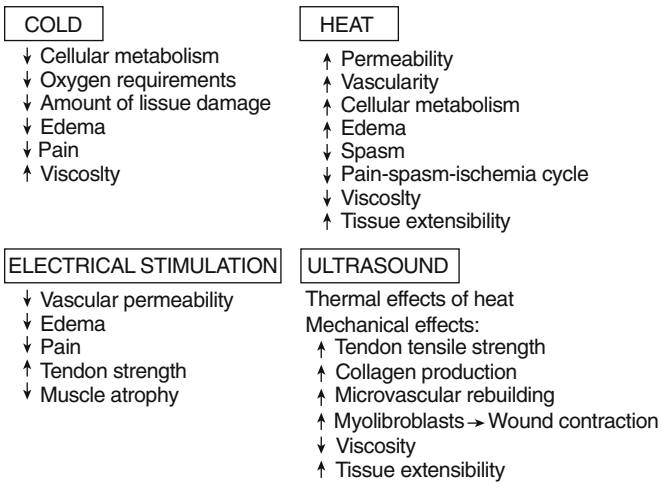

FIGURE 9-4. Effects of physical therapy modalities on tissue response to injury, adapted from Houglum PA (1992).

some studies have not been universally replicated [13,109].

Medication

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the drugs most commonly used by athletes [4,31,42,67,92]. The effectiveness of NSAIDs in chronic tendon disorders remains questionable [42]. Their most important effect is presumably not anti-inflammatory but analgesic [4,31,92]. In addition, the role of NSAIDs concerning wound healing remains questionable [42]. In patients with insertional tendinopathies, NSAIDs may be used to facilitate rehabilitation and to treat associated inflammatory processes like bursitis or paratenonitis. Topical diclofenac has recently been shown to be effective in tennis elbow [16]. In this way, oral administration and adverse effects may simultaneously be decreased. "As much as needed but as little as possible" should be the guiding principle.

The use of corticosteroid injections should remain a form of adjunctive therapy. Almekinders and Temple state the early pain relief with steroids but remind of the uncertain final outcome, since recurrences are common [4]. Overall, corticosteroid injections have lost favor because of their inhibition of collagen synthesis and their potential deleterious effect when injected into the tendon [42]. In case of persistent pain and inability to perform a rehabilitation program, corticosteroid injections may be indicated. In any case, the guidelines for steroid administration must be respected. Corticosteroids should not be injected into tendons, no more than 2 injections spaced several weeks apart should be given, repeat injections should be used only after at least partial relief, and they should not be used after an acute injury, before a competition, or in the presence of infection [92]. The effect of corticosteroid injections is usually short lived, i.e. less than 6 weeks. Furthermore, corticosteroid injections should be accompanied by a few days of rest and gradually increased exercise afterwards.

New research dealing with neuropeptide activity and gene therapy in tendon ailments provides a better understanding of the underlying pathology and innovative management approaches [1,112]. New techniques, such as tissue engineering, offer the potential to improve tendon healing. These concepts are based on the manipulation of cellular and biochemical mediators to affect protein synthesis and improve tissue remodeling. Recently, application of growth factors and gene transfer techniques have shown promising results, and may become effective therapies. Gene-activated matrix (GAM) was the first gene therapy designed specifically for tissue engineering applications. GAM could serve as a platform technology for local gene delivery to enhance soft tissue healing. Cell therapy involves the introduction of mesenchymal progenitor cells as a pluripotent cell source into the healing environment. The combination of cell therapy with growth factor application via gene transfer offers new avenues to improve ligament and tendon healing [14,112,155].

Surgery

Surgery has become an accepted therapeutic option for failed nonoperative care of insertional tendinopathies [50], but should be considered a last resort [44], especially when one appreciates the confirmed degenerative origin of insertional tendinopathies, and the fact that improvement of nonoperative results over a long period of time is not uncommon [54].

Leadbetter et al. itemized 7 goals for surgery in tendon overuse injuries. These apply to insertional tendinopathies [50]:

1) To improve tissue structure and strength by inducing scar tissue.
2) To remove aberrant tissue, i.e. granulation tissue, calcific deposits, and degenerative or necrotic tissue.
3) To encourage revascularization of injured tissue.
4) To relieve extrinsic pressure, e.g. bony spurs.
5) To relieve tensile overload.
6) To discover and repair relevant tears.
7) To replace or augment injured tendon structure.

The surgical techniques available to achieve these goals include the following: Intratendinous or paratendinous excision, decompression, synovectomy or bursectomy, longitudinal tenotomy, tensile release, repair, and tendon transfer or graft [92]. The end result of surgical procedures is not *restitutio ad integrum*. Both patient and physician must take into account that a scarred, repaired tendon is probably prone to reinjury lifelong. Consequently, the importance of rehabilitation cannot be overemphasized. Overall, a success rate of 75% to 85% of surgery for insertional tendinopathies has been reported [44,50,92].

The enormous variety of surgical procedures for specific insertional tendinopathies exemplifies the lack of generally accepted management regimens. Operative procedures for insertional tendinopathies require repeat surgery in 10% to 15% of patients, showing the delicate balance between success and failure [92].

In general, most insertional tendinpathies are degenerative disorders often due to overuse. Despite thorough histopathological investigations of OTJs, little is known of the biomechanical properties and functional behavior of the OTJ under various loading conditions *in vivo.* Biochemical investigations of overuse-related tissue degeneration, studies of tendon avulsions, and biomechanical investigations of overuse effects on OTJs will foster a better understanding of insertional tendinopathies.

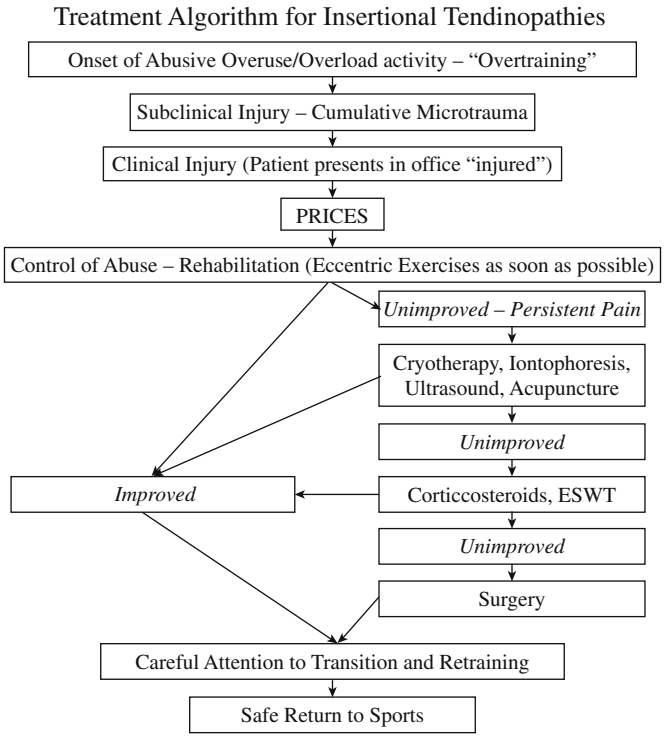

FIGURE 9-5. Algorithm for the management of insertional tendinopathies.

More aggressive postoperative rehabilitation has become a mainstay of management in an attempt to return patients faster to a high level of sports activities. Figure 9-5 summarizes the description of management modalities for insertional tendinopathies.

Rotator Cuff Insertional Tendinopathy

The most common cause of shoulder pain is soft tissue dysfunction. Rotator cuff tendinopathy and microtears are therefore regarded as the primary component of subacromial pain syndrome [56,108]. The supraspinatus tendon is the most commonly affected by wear and tear of all rotator cuff tendons. Consequently, insertional tendinopathies of the supraspinatus are most common. The supraspinatus tendon has a relatively hypovascular zone close to its insertion. This "critical zone" is subjected to great tensile stresses and friction [54,56]. In addition, the OTJ is also a weak link in the bone-tendon complex [94].

Codman already suggested in 1934 that chronic shoulder problems are of degenerative origin [21]. Sano et al. have described the width of the sulcus between humeral articular cartilage and supraspinatus tendon insertion as a useful indicator for the integrity and tensile strength of the supraspinatus tendon. Accordingly, an evaluation of the sulcus width, either arthroscopically or by MRI, can have prognostic significance as it correlates with the severity of degenerative changes [50].

Aging, diminished vascularity, overuse, microtraumata, subacromial pathologies, impingement, and calcification are various reasons for the multicausal pathology in rotator cuff tendinopathy [31]. Tendon tears are found in the so-called critical zone of the supraspinatus tendon and at the OTJ. Tendon degeneration has been suggested as a main pathogenetic factor of rotator cuff tears [69,76,94]. Since degenerative changes are more common disorders in patients older than 50 years, and rotator cuff tears in cadaveric studies increase with age [58], traumatic rotator cuff tears in athletes must be distinguished. Finally, both disorders demonstrate underlying degeneration, but the mechanisms of injury are different. Degenerative rotator cuff tears can occur during daily activities and are often asymptomatic [31,54], whereas traumatic tears in athletes result from tendon failure due to overstrain [45].

The most noteworthy clinical findings are stiffness, weakness, crepitus on passive glenohumeral motion, and pain during movement or at rest [76,85,110]. Functional muscle tests help to locate the rotator cuff insertional tendinopathy. As this entity infrequently exhibits unequivocal symptoms, imaging techniques are helpful for diagnosis.

Ultrasonography and MRI help to detect rotator cuff insertional disorders [31,85,92]. MRI arthrography is very sensitive for the identification of even very small partial tears. The question is whether nearly asymptomatic cuff pathology should be detected at all, because the point for therapeutic implications has not yet been convincingly made.

Initial management of partial or full-thickness rotator cuff tears—if symptomatic—should follow the management regimen described above, so that edema formation can be decreased and further injury is reduced [31]. Depending on the patient's symptoms and activity level, a nonoperative or operative approach is to be considered.

Operative management for rotator cuff tears offers a great variety of procedures, both arthroscopic and open. Excellent and satisfactory results range between 70% and 90% [85].

Tennis Elbow

Tennis elbow is one of the most common clinical problems in sports medicine, already described in 1873 [91]. In 1883, the term lawn tennis elbow was coined [60].

The problem generally arises from tendinopathy of the attachment of the tendon to the extensor carpi radialis brevis muscle at the lateral epicondyle. The diagnosis can be straightforward, although there are some other differential diagnostic options, such as cervical radiculopathy, referred shoulder pathology, radial tunnel syndrome, or posterior interosseous nerve entrapment. The most characteristic symptoms of tennis elbow are pain and tenderness at the lateral epicondyle of the humerus. The pain may radiate distally and, more rarely, proximally. The range of motion of the elbow is usually full except in chronic, severe cases [19]. Functional and provocative tests are of great diagnostic value. The "coffee cup test," i.e. picking up a full cup of coffee, is almost pathognomonic for tennis elbow. Pain from resisted wrist or middle finger dorsiflexion with the elbow fully extended is typical. The area of tenderness pinpoints the affected extensor muscle [19,63,72,82]. Grip limited by pain is another useful index, and dynamometry can quantify these functional strength deficiencies objectively [66].

Management is based on a progressive, controlled exercise program, which is the key to stimulate the biological healing response. The main part of this training program includes eccentric action and some stretching. Initially this exercise program needs supervision, as it is difficult to dose correctly. Counterforce bracing has some good effect clinically. Among modalities, acupuncture seems to be a possibility. Some studies report good results with ESWT [13,29,88], but the scientific evidence is still not fully convincing. Cortisone injections are the last line of conservative management. Their effect is usually short lived. These injections should therefore be combined with some rest and gradually increased exercises. Surgery may be indicated in 5% to 10% of patients, and consists of excision of the pathology in the extensor carpi radialis brevis. This can be completed by decortication of the anterior lateral condyle for vascular enhancement [46,63, 72,92]. Figure 9-6 shows the intraoperative appearance of tennis elbow. The success rate for surgery is usually higher than 80% [19,25,47,63,64,72,148].

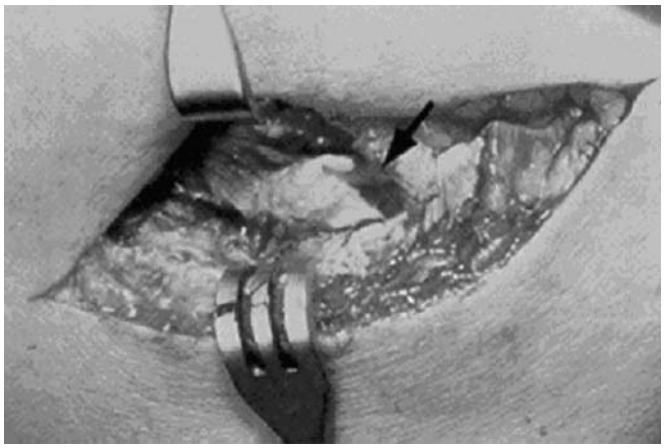

FIGURE 9-6. Partial interstitial tear of extensor carpi radialis brevis tendon in the area of tendinosis; the lateral epicondyle elbow.

Jumper's Knee

Jumper's knee is a classic overuse disorder [23] with microtearing of the patellar tendon along the knee extensor mechanism between the upper patellar pole and the tibial tubercle. The lower pole of the patella is affected in 65% of cases, with the upper pole (25%) and the tibial insertion (10%) less commonly involved [23,31]. Interestingly, the outcome of management for insertional tendinopathy is not as good as for disorders of the main body of the patellar tendon [42].

Jumper's knee is more frequent in athletes with vigorous and repeated exertion of the quadriceps muscle [129,130]. Therefore, activities such as basketball, volleyball, American or European football, tennis, or track and field (long jump, high jump, hurdles) are most commonly affected [42,44,119,129]. Table 9-2 shows a comparison of the tendinosis classification from Nirschl [63] and the jumper's knee classification from Blazina [119]. Despite the different dates of publication and purpose, the similarities are striking. Another useful instrument for evaluation of patellar tendinopathy is the more differentiated VISA (Victorian Institute for Sports Assessment) score [131].

It is important to correctly diagnose patellar tendinopathy as early as possible (Stage 1), so that progression and chronic disease may be prevented. Patients often report an insidious onset of symptoms and a dull anterior knee pain. Tenderness at the inferior patellar pole is the key finding. It is most distinct in full knee extension, and may be decreased in knee flexion [42]. In

TABLE 9-2. Comparison of tendinosis and jumper's knee classifications, adapted and modified by permission

	Tendinosis classification (Nirschl, 1992)	Jumper's knee classification (Blazina, 1973)
Stage 1	Temporary irritation	Pain after activity, no functional impairment
Stage 2	Permanent tendinosis—less than 50% tendon cross section	Pain at beginning of activity, disappearing after warm-up, reappearing after activity
Stage 3	Permanent tendinosis—greater than 50% tendon cross section	Pain during and after activity with functional impairment 3a: able to train and play 3b unable to train and play
Stage 4	Partial or total rupture of tendon	Complete tendon rupture

more severe stages, clinical examination may reveal pain during resisted knee extension.

Many ultrasonographic studies have been performed [132–142], and MRI can also be a useful diagnostic tool. However, ultrasonograms and MRI scans do not always correlate with pathologic appearance and clinical findings [55,115]. Therefore, clinical examination and imaging must support each other to establish the diagnosis of patellar tendinopathy.

The biomechanical analysis of patellar tendinopathy needs further investigation. The etiology of insertional patellar tendinopathy is widely discussed, and it remains to be elucidated whether tensile strains [23,31,147] or compressive loads and impingement [123,146] are the major causative factors of disease.

There is a surprising lack of scientifically proven management options [42,92,114,115,121,123]. In the early stages, the management modalities described above are generally effective, and local corticosteroid injection should be avoided [115,143]. Careful eccentric exercises should be included as soon as possible in the rehabilitation program [24,42,44,137,144]. High eccentric loads during training (e.g. squatting) should be avoided until recovery [115]. Stretching exercises should accompany the strengthening program to encourage flexibility and adaptation of muscle-tendon units. For basketball and volleyball players, landing from a jump on two feet can be a simple and effective step to reduce wear and tear of the patellar tendon.

Surgery for patellar tendinopathy includes stripping of the paratenon, removal of pathological tissue, longitudinal tenotomies, and drilling of the bone-tendon junction [23,42,115,147]. Recently, arthroscopic procedures have been described as an alternative surgical approach, but the effectiveness of arthroscopic over open surgery has not been proven [87,145,149]. Recommendations for surgery range from 6 to 12 months of unsuccessful conservative management, and suggest recalcitrant Stage 2, Stage 3, or only Stage 4 for surgical management [23, 50,115,147]. Therefore, despite relatively high surgical success rates, the mainstay of management remains conservative management, and the sports physician must decide with the patient whether surgery is indicated.

Insertional Achilles Tendinopathy

The Achilles tendon is the largest tendon in the human body. Insertional tendinopathies comprise about 10% to 25% of Achilles complaints [27,100,150]. Insertional Achilles tendinopathy is caused by chronic degeneration within the tendon insertion onto the calcaneus, commonly presenting as an overuse syndrome [120]. It is most common in middle- and long-distance running, dancing, soccer, and tennis [27,118,151], with an incidence in runners of about 10% [62]. Training errors are very common for athletes with Achilles tendinopathy. A change in surface, a sudden increase in mileage, hill running, and improper stretching techniques often exacerbate the pain [27,62,118]. There is a high association of insertional tendinopathy with retrocalcaneal bursitis, and up to 60% of patients also have Haglund's deformity [62,118].

Tenderness directly at the Achilles tendon insertion is typical. Pain may be aggravated by passive dorsiflexion, and a loss of passive dorsiflexion is not uncommon [117]. Sometimes even a palpable defect in the tendon may be noted [62]. Hyperpronation and forefoot varus are commonly associated with insertional Achilles disorders [148]. Therefore, gait analysis is a useful tool in diagnostics.

Radiographs frequently demonstrate calcification or ossification of the Achilles tendon insertion. Ultrasonography and MRI are useful to evaluate Achilles tendon pathology [27,39]. However, both methods are of limited use regarding surgical decision-making, since the pathology is easily detected clinically. However, imaging may be used as prognostic indicator as it shows the severity of tissue alterations [5]. Figure 9-7 shows typical changes in the MRI at the Achilles tendon insertion.

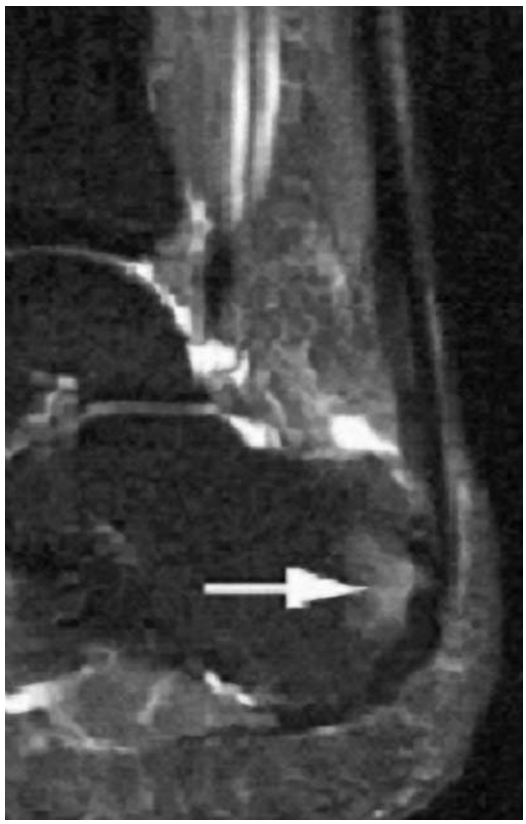

FIGURE 9-7. Sagittal STIR image shows increased signal intensity (arrow) in calcaneal bone marrow as sign of reactive edema. Also, retrocalcaneal bursae and adjacent Kager's fat pad show increased signal intensity.

The management scheme for the insertional tendinopathies described above applies very well to the Achilles tendon. A sleeve or heel pad can provide a simple and inexpensive alleviation of pain [62,148]. Finally, the choice of appropriate footwear, possibly antipronation shoes, is essential to treat the condition and prevent recurrence.

There are many surgical approaches to deal with insertional Achilles disorders, and evaluation of these goes beyond the scope of this chapter. Regardless of the surgical approach, it is important to debride tissue abnormalities, resect a potentially inflamed retrocalcaneal bursa, and to remove Haglund exostoses or other calcifications [62]. Combined with current techniques of surgical repair and rehabilitation programs, innovations like growth factor therapy [153] or low-energy photostimulation [154] could improve the outcome of athletes with Achilles tendon injuries.

Conclusions

Despite—or possibly because of—so much disagreement about the etiology and management of insertional tendinopathies, this field needs much more research [121].

A well-planned rehabilitation program with stretching and strengthening exercises is the mainstay of management to promote healing and prevent further injury. An injured tendon does not regenerate, but heals by formation of inferior scar tissue. For patients who fail conservative management, a variety of surgical procedures exist with acceptable success rates. Further research concerning the effectiveness of management protocols is necessary, so that scientifically based guidelines can be developed. In addition, new research areas such as tissue engineering, gene therapy, neurotransmitters, neuropeptides, growth factors, and photostimlation may yield promising results for future therapeutic implementation.

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10
Tendon Avulsions in Children and Adolescents

Sakari Orava and Urho Kujala

Introduction

During growth, the apophyses and insertion sites of tendons and muscles are weaker than the tendons and muscles themselves, and bones. At these growth areas, therefore, avulsions of tendons and muscles or avulsion fractures may occur [1], especially during physical activity, including school and competitive sports. These injuries may occur also as a result of direct contusion, fall, or twisting injury. Some of these injuries cause sudden severe symptoms with pain, swelling, disability, and loss of function [2–4]. In partial avulsions, the symptoms are minor, and the correct diagnosis is frequently delayed. In these cases, often ectopic calcification is observed at a later date, as a consequence of periosteal new bone formation in the hematoma at the site of the lesion [1,5]. This heterotopic bone growth may hamper the function of the limb, limiting range of motion, or by the friction of soft tissues rubbing over the prominence. Fibrotic nonhealed avulsions cause prolonged problems, prevent maximal performance, and prompt further examination in greater depth.

Principles of Diagnosis and Management

The diagnosis of a tendon avulsion is usually easy. A careful history and physical examination are usually complemented by plain radiographs. At times, only special projections show the avulsed fragment [6]. Further diagnostic procedures are seldom necessary in the acute phase. However, in patients with long-standing history, ultrasonography, bone scan, computed tomography (CT) scan, or magnetic resonance imaging are needed for a more precise diagnosis and to plan management [7].

In most patients with tendon or muscle insertion avulsion, management is conservative [8,9]. Immobilization in a plaster cast, elastic bandage, crutches, modified rest from physical activity, cold packs, and oral analgesia are usually sufficient. Rarely, surgical evacuation of the hematoma and fixation of the avulsed fragment may become necessary [3,10]. After surgery, immobilization to allow soft tissue and bone healing is required. Rehabilitation to return to the preinjury level of performance is important. Follow-up of the patients is needed for long enough to detect possible complications and the rare growth disturbances that can follow avulsions, regardless of the management method [9,11]. Early recognition of the injuries and initiation of appropriate management can prevent prolonged disability and later deformity, and help to return the young athletes to sports.

Avulsion Site and Type

There are several reports of different avulsion lesions [1,4,8,10–13]. Almost all of the tendons of the human body have been reported having been avulsed, mostly in children, adolescents and young adults [1]. The most common avulsions are those of the finger extensors at the distal phalanges (mallet finger); patellar tendon avulsion at the tibial tuberosity; hamstring tendons at the ischial tuberosity; and avulsions at the anterior spines of the pelvis and at the peroneus brevis tendon insertion at the fifth metatarsal bone [1]. Probably, avulsions at the iliac crest apophysis [14] or the triceps tendon at the olecranon [7] are comparatively rare. Though most avulsions occur in children and adolescents, they are seen at all ages.

Upper Extremity

In young athletes in throwing and "overhead" sports (such as baseball, javelin, tennis, and volleyball), apophysitis may occur at the medial humeral epicondyle, the site of the common flexor muscle insertion [5]. Little League elbow encompasses medial epicondyle apophysi-

tis or partial tear, and/or a lateral radiohumeral chondral lesion from repeated compression injury during throwing [15]. The medial epicondyle may separate and remain nonunited until adolescence or adulthood. It may require later surgery with removal of the loose fragment.

Avulsion of the triceps tendon is uncommon, typically occurring in skeletally mature individuals. It can also occur in adolescents [7]. Magnetic resonance imaging is useful in confirming the diagnosis. Stress fractures of the tip of the olecranon and apophysitis of the olecranon have been described in young javelin throwers [16].

Distal biceps tendon avulsion in young individuals is very rare. The diagnosis is not always easy, and magnetic resonance imaging helps to evaluate the severity of the injury and to plan management. Surgical reinsertion gives the best results in managing this injury [13,17]. Proximal avulsions of the tendon of the long head of the biceps may occur intra-articularly as a superior labrum anterior-posterior (SLAP) lesion. This injury has to be considered in the differential diagnoses of shoulder sports injuries seen in adolescent athletes [18]. The management is arthroscopic metal or bioabsorbable anchor fixation.

Small partial avulsions in the wrist and hand of young athletes occur often [1], and are sometimes difficult to detect clinically and radiographically [15]. With total tendon avulsions, loss of function makes the diagnosis easier. In "mallet finger," both avulsion fractures and tendon avulsions occur. They should be treated without delay with a finger extension orthosis or by surgery. Recognition of injury patterns in sports, with early activity modification, can prevent deformity and disability from all upper arm injuries [15].

Pelvis

Anterior iliac spine avulsions are classical injuries to adolescent athletes. They have been reported in the superior and, less frequently, in the inferior anterior iliac spine [2,9,11,19]. The involvement of the apophysis ranges from painful apophysitis to full avulsion fracture [12]. Most of the avulsions can be treated conservatively with rest and/or immobilization. Surgery may be required when there is major displacement or a large bony fragment [2,10]. In some patients, long-lasting functional disability remains due to a prominent bone fragment or new bone formation. Limitation of hip joint flexion may follow a displaced, malunited fragment of the anterior inferior iliac spine. We have performed surgical excision of large ectopic calcifications after avulsions of the inferior anterior iliac spine with limitation of hip joint flexion.

The ischial tuberosity can avulse by traction of the hamstring tendons. Apophysitis, partial avulsion, and large bony avulsion are different types of this avulsion injury [20,21]. Apophysitis usually occurs to 13- to 15-year-old athletes, and avulsion fractures to 14- to 16-year-old athletes, but they are sometimes seen in older individuals [22]. Local pain, especially on stretching, is typical, and hampers active exercise. A large hematoma of the posterior thigh can occur after bony avulsions. Bony avulsions with a diastasis greater than 3 cm are treated surgically. Other injuries usually heal with conservative management [9,10,21,22]. Sometimes there are problems in the differential diagnosis. Bahk et al. described neoplasm simulating avulsions in 11- and 15-year-old boys [23].

Avulsions of the iliac crest are rare, but can be seen in adolescent athletes [24,25]. These are usually partial and can be treated conservatively. Healing by ossification usually occurs, but may take several months.

Avulsions of muscle or tendon insertions of the pubis and the lesser trochanter are also rare [11], and normally heal with rest, seldom causing later problems.

Knee

In the adolescent knee, avulsion of the intercondylar eminence of the tibia is a type of ligament injury, and is beyond the scope of this chapter [26]. Avulsion of the adductor tubercle is seen associated with medial capsuloligamentous injuries [19].

Complete tears of the quadriceps tendon and patellar tendon usually occur in older individuals, but have been seen occasionally in high-power sports events, such as high jump, basketball, and weightlifting [13]. Total transverse fractures of the patella have been reported to occur with maximal jumping or landing injury mechanisms. Patellar avulsions through the proximal or distal apophysis have been described [4], both in patients with and without jumper's knee.

Avulsion fractures or apophyseal injuries of the anterior tibial tuberosity occur mainly during sport activities, and are due to high strains exerted on this region by the eccentric action of the knee extensor muscles [8,27,28], and have been reported in adolescent athletes both with and without Osgood-Schlatter lesions [27,29–31]. Usually, avulsion fractures are partial [8], but complete bony avulsion may also occur [28,32], as well as true distal patellar tendon avulsions [31]. Konsens and Seltz reported fractures and tendon ruptures through large patellar tendon ossicles following Osgood-Schlatter disease [33]. In mild displacement, following closed reduction of the fragments, immobilization in a cast for 3 to 4 weeks is recommended [8,30]. In some patients with partial avulsion, rest from physical activity with elastic bandage has been used successfully as the only management. Displaced fractures have been treated surgically by internal fixation with screws, Kirschner wires (with or without a metal wire tension band), and with sutures through drill holes, with postoperative immobilization in a plaster cast for 4 to 6 weeks [3,27,28,30].

Foot and Ankle

Avulsions of the Achilles tendon with a bony fragment are rare [19]. These injuries need a well-planned surgical repair. The insertion site should be reconstructed, and the bony prominence of the superior calcaneal corner should not cause any anterior irritation to the tendon (see Figures 10-1 and 10-2).

Avulsion fracture of the base of the fifth metatarsal is usually a relatively benign injury [34]. Sometimes, the diagnosis is delayed, and the fracture is not seen in conventional radiographs of the foot [6]. However, it will usually heal with rest from physical activity for one month. Elastic bandage can be used for the first week or two. Avulsion of the peroneal tendon from the base of the fifth metatarsal can be bony, periosteal, or a pure tendon insertion avulsion [1]. In avulsion fractures with large diastasis and in tendon avulsions, surgical management ensures the full force of eversion of the foot [35].

Avulsions of the tendon of the tibialis posterior from the navicular are rare, the diagnosis can be difficult, and surgical management can be required [34]. Avulsions of foot extensor or flexor tendons seldom occur in athletes. Loss of functions is usually detected right after the injury, and early surgical reinsertion gives good results [34].

Tibialis anterior tendon avulsion from its tarsal insertion may occur, but usually the tendon rupture occurs at the anterior aspect of the ankle of middle-aged patients [34]. Extensor and flexor tendon avulsions at the insertion sites of toes are rare.

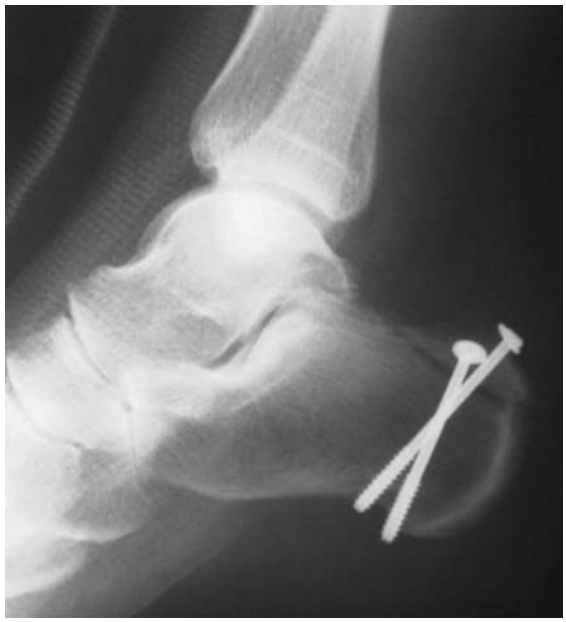

FIGURE 10-2. Avulsion of the superior corner of the calcaneus in a 19-year-old female dancer following percutaneous fixation with two partially threaded, cannulated cancellous screws inserted at either side of the Achilles tendon. (Courtesy of Prof. Nicola Maffulli.)

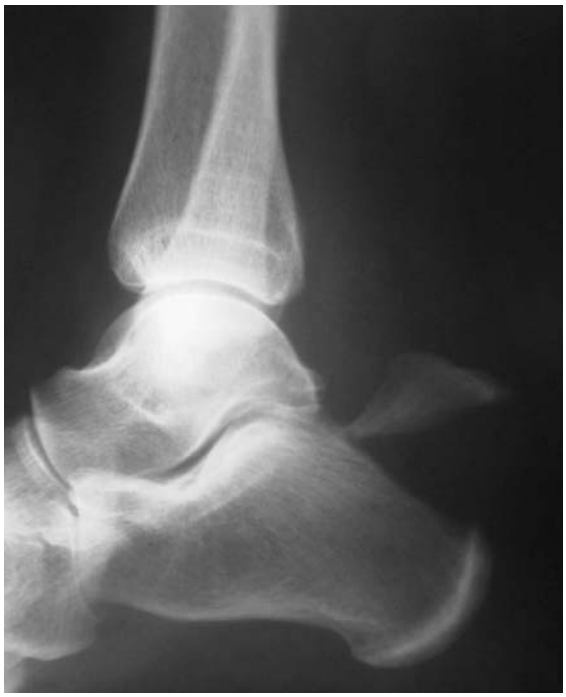

FIGURE 10-1. Avulsion of the superior corner of the calcaneus in a 19-year-old female dancer. (Courtesy of Prof. Nicola Maffulli.)

Conclusions

Tendon avulsions as a group are not rare. Although tendon avulsions occur in all age groups, adolescent athletes especially suffer from these injuries. The apophyses in children and adolescents are weaker than other supporting structures around them [1]. In the immature skeleton, other epiphyseal injuries are seen with the same injury mechanisms that cause ligamentous or bony lesions in adults [36]. Some of the osteochondroses in active young athletes, together with the strains of training, may weaken the apophyses, and increase the risk for avulsion fractures [5]. The diagnosis of a tendon avulsion or an avulsion fracture is usually easy. The management is planned according to the type, site, and degree of the injury. It is usually conservative, but surgery may be needed too. When a bony or cartilaginous avulsion occurs around the age of full ossification, conservative management usually is successful. Later, in instances of purely tendinous avulsions, surgery is more often indicated.

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11
Tendinopathy in the Workplace

Leo M. Rozmaryn

Introduction

Until relatively recently, little attention has been paid to the millions of workers who go to work each day and perform the same highly repetitive tasks for years at a time. An assembly line worker may repeat the same task 25,000 times per day [1]. Each exertion requires a specific movement of the upper or lower extremity, usually with the maintenance of a static posture of the trunk, head, and neck. Over time, the amount of physical effort required to accomplish such seemingly mundane tasks is extraordinary. With millions of people at computer keyboards each day, it is not surprising that overuse syndromes or repetitive strain injuries have come into media focus and attention.

Repetitive strain injuries are disruptions of muscles, tendons, bone, or nervous system precipitated or exacerbated by repeated forceful exertions, awkward posture sustained for a long time, surface contact stresses, vibration, or cold. Jobs that have multiple risk factors have a greater likelihood of causing or contributing to musculoskeletal disorders depending on the magnitude, duration, and frequency of the exposure to each risk factor [2].

Patients with upper extremity repetitive strain injuries present with pain, usually in the neck, shoulder, arm, or hand; fatigue, either generalized or localized; and weakness, paraesthesias, loss of dexterity, depression, and loss of sleep. Many patients relate this to the duration and intensity of their work. Symptoms may develop over weeks, months, or years, and patients commonly cannot pinpoint a specific time of onset. Symptoms may be poorly localized, nonspecific, and episodic, and the causes may be multifactorial. These patients may initially appear to suffer from simple fatigue. The difference between simple fatigue and repetitive strain is related to the duration and intensity of the symptoms. Fatigue can occur after a work shift and is short lived. With repetitive strain injuries (RSI), recovery between work shifts does not occur, and patients begin their day or week with pain [3].

The Occupational Safety and Health Administration (OSHA) has defined several conditions as "work-related musculoskeletal disorders" (WMSDs) caused by workplace stressors [4]. These include carpal tunnel syndrome, rotator cuff tendinopathy, de Quervain's disease, trigger finger, and lateral and medial epicondylitis.

The term tendinopathy denotes pain involving tendons or their surrounding structures, which at times can be inflamed, usually caused by repeated or forceful exertion by the affected part. Tendinopathy is usually made worse by performing an activity in an awkward position.

These conditions have now been recognized as the leading chronic work-related musculoskeletal disorders, and have served as the basis for the proposed ergonomic standard that will be discussed later. This chapter examines the epidemiology of these problems and the cost to society as a whole. Newer evidence for work relatedness and occupational tendon pathophysiology will be discussed, and we shall also discuss how ergonomics relates to the correction and prevention of these issues, focusing specifically on tendinopathy. There is much controversy about the cost-effectiveness of ergonomic programs. Follow-up evidence for cost effectiveness will be presented.

The Scope of the Problem—Epidemiology

Work-related musculoskeletal disorders account for nearly one-third of all occupational injuries reported in the US. In 1997, employees lost more than 600 000 workdays [5]. Between US $20 and $30 billion is spent each year on workers' compensation claims for repetitive strain injuries of the neck and upper extremity. Taken together, these represent more than 50% of the cost of all occupational injuries [6]. It is estimated that the total cost of treatment nationwide for carpal tunnel syndrome

exceeds $3.5 billion. The average carpal tunnel release costs US $27,000, including the medical and legal costs, and intangible costs such as lost productivity [7].

Workers with severe symptoms can face permanent disability that prevents them from returning to gainful employment, and even everyday tasks can cause disabling pain.

The fundamental question is why so much attention is being paid to repetitive strain injury now, when workers have been toiling on assembly lines for nearly 100 years. The answer may lie with the dramatic rise in the reporting of such injuries, which has resulted in skyrocketing health costs in dealing with these patients. The Bureau of Labor Statistics reported in 1997 that in private industry alone there were 705,800 illness claims for repetitive strain, which represents a 2,700% increase since 1982. Of these, more than half were due to overexertion in lifting, 15% were due to overexertion in pushing and pulling objects, and 10% to holding, carrying, and turning objects. About 92,500 injuries were due to upper extremity repetitive motion. These include data entry and repetitive grasping [8].

Large epidemiological studies of cumulative trauma disorders indicate a wide variety of workers who are "high risk" for the development of these conditions. These include meat packers, cashiers, data entry clerks, musicians, construction workers, electricians, cake decorators, postal workers, assembly workers, punch press operators, and automobile workers [9]. The estimated probability that a worker will experience at least one work-related musculoskeletal disorder during a working lifetime of 45 years is 24 to 800 per 1,000 employees, depending on the industry sector [10].

The use of computers has dramatically risen during the past 15 years. With increased pressure to produce more in less time, many office tasks have been reduced to their simplest components, and individual workers may have to perform fewer tasks at ever increasing rates. The mechanics of computer use differ significantly from those of the typewriter. The typewriter by its nature demands the necessary steps in paper handling and adjustments. The computer user has no such break-time from repetitive keying. People who use computers for more than 4 hours at a time are at 3 times the risk for developing shoulder, arm, or hand pain. The odds are significantly higher for supermarket cashiers and assembly line meat packers.

The Functional Anatomy of Tendons

A typical tendon extends from the myotendinous junction to the bone tendon junction. Tendons are composed of dense connective tissue with regularly arranged collagen fibers of great tensile strength. In general, tendons: 1) extend the reach of muscles and permit the muscle to pull through fibro-osseous tunnels; 2) enable the pull of a muscle to be focused onto a single or multiple sites; 3) eliminate the need for unnecessary length of muscle between the origin and insertion, allowing the length of the muscle belly to be appropriate to the amount of movement required. Thus, the longer the muscle belly, the greater the range of motion; 4) change the pull of a muscle by wrapping around bone pulleys; (5) reinforce the underlying joint capsule; (6) have elasticity so that energy is stored in the muscle-tendon units when the limb is passively stretched in the opposite direction of the tendon action; and 7) hold other tendons in position [11].

As a rule, tendons in the upper extremity are attached immediately distal to the joint that they move. Although this causes a mechanical disadvantage, it is compensated for by a greater speed of action and increased efficiency and excursion of the limb. Typically, the entheses are attachment points of tendon to the bone, and contain a high concentration of fibrocartilage [12]. These allow the transitional tissue to maintain high tensile strength in a relatively avascular environment. The tendon microstructure is modified where it changes direction and wraps around a bone pulley. At the pulley, both the tendon and the periosteum are fibrocartilaginous where compressive forces are maximal. Fibrocartilage is usually restricted to the side of the tendon facing the compressive structure [13]. This is particularly prominent in the fingers, where the tendons press against the fibrous pulleys and where the extensor tendons form the dorsal part of the finger joint capsule. The fibrocartilage may arise through metaplasia of the tendon cells [14].

Retaining Ligaments

Flexor and extensor retinacula in the wrist hold the tendons of the forearm and the muscles in position. Pulleys and fibrous sheaths in the fingers hold the flexor tendons in place and prevent them from moving out of line and bowstringing when flexing. These pulleys may be torn or avulsed by excessive load on the tendons. Pulleys may also be too small for the tendons, leading to constriction and development of a trigger finger. Retinacular and fibrous pulleys may contain fibrocartilage similar to the compressive fibrocartilage of tendons. Indeed, they may contain even more fibrocartilage than the tendons themselves. The fibrocartilage here may also change and respond to changes in mechanical stimuli.

Synovial Sheaths and Bursae

A tendon is held by a retaining ligament and must be able to glide freely beneath it. At such locations, the tendons are surrounded by synovial sheaths or by paratenon. These are closed sacs that contain a thin film of lubricat-

ing synovial fluid. These sheets often extend beyond the limits of the retaining ligament, so that the tendons can slide beneath them, and may surround a single tendon or a group of tendons. This synovial layer may also provide nutrition by diffusion to the tendon, especially in the avascular areas of the tendon. This may be a more important source of nutrients than blood vessels in general. Thus, the tendons are hydrodynamically lubricated. The friction caused by fast, repetitive motion of tendons within the sheath can result in tenosynovitis [15].

Physiology of Tendon Strain

The primary function of tendon is to transmit forces from the muscle to the bone. Accordingly, its principal injuries involve forces causing stretch deformation or inadequate recovery (i.e., return to resting length) on the one hand, and frictional damage due to shear and extrinsic compression on the other. The tendon is subject to both uniaxial tensile forces from muscles and transverse forces from anatomic pulleys, bursae, and extended range of motion. Tensile and transverse forces produce shear and influence tendon gliding. These forces across the tendons are increased during prolonged awkward or extreme positions at a joint such as the wrist [16].

As muscles contract, tendons are subject to mechanical loading and viscoelastic deformation. Tendons have excellent resistance to tensile loading, and their elastic properties enable them to move around turns, such as in the hand. When collagen bundles are placed under tension, they elongate without significant increase in stress. With increased tension, they become stiffer in response to loads. If the load on these structures exceeds the elastic limits of the tissue, permanent changes occur [17]. The ultimate tensile strength of normal tendons is about 50% that of cortical bone. If recovery time between contractions is too short, plastic deformation can result, along with permanent changes that decrease the tendon's ultimate strength.

Tendons also exhibit relaxation and creep. When a tendon is subjected to prolonged elongation and loading, the magnitude of tensile forces will gradually decrease, and the length of the tendon will gradually increase [18]. In repetitive loading, the tendon exhibits these properties and then recovers if there is sufficient recovery time. If the interval between loading does not permit restoration, then recovery can be incomplete, even if the elastic limit is not exceeded [19].

When tendons are subject to perpendicularly oriented compressive loading, as happens when they are sliding around fibrous or bony pulleys, friction is generated, causing a shearing force. This is seen commonly in the hand and wrist, especially in nonneutral wrist postures. For example, the compressive forces on A1 pulleys rise dramatically from neutral to full flexion of the wrist. Tendon friction is proportional to the axial tension of the tendon, the coefficient of friction between the tendon, and the adjacent surface of the angle of the tendon as it turns around the pulley. This may be the cause of surface degeneration in the tendon. Internal degeneration may result from friction-induced internal heat generation [20].

Paratendinopathy (tenosynovitis) is mainly inflammation of the paratenon. Signs and symptoms include localized pain, swelling, warmth, and tenderness. Tendinopathy involves intratendinous degeneration with fiber disorientation, scattered vascular ingrowth, tissue necrosis, and calcification. Tendon nodularity may be noted, but swelling of the tendon sheath is absent. Paratendinopathy may be observed with tendinopathy. Paratendinosis, inflammation, and intratendinous nodularity are possible. Tendinopathy can range from a tear with inflammation and acute hemorrhage to chronic degeneration [21].

Clinically, tendon compression in the hand manifests as stenosing tenosynovitis initially. There is impaired motion, tenderness, and pain with resisted contraction of passive stretch, swelling, and crepitus. With time, the tendon swells and thickens from tendon fibril disruption, partial laceration, engorgement, and diffusion of metabolites. Ultimately, these limit the normal passage of the tendon through fibro-osseous canals, with triggering. The tendon becomes nodular with fusiform swelling, and fibrocartilaginous metaplasia or fraying of the tendon. When the tendon load is great or highly repetitive, there is insufficient recovery time between deformations for the tendon to return to its resting length, and viscous strain can exceed elastic strain, causing tendon deformation. A different injury mechanism occurs when tendons and tendon sheath are forced over hard, anatomic surfaces producing paratendinopathy, synovitis, or degeneration due to lack of blood flow at the site of compression. Impaired circulation, bony compression, and degenerative changes are typical of rotator cuff injuries where tendon insertions on the greater tuberosity can be compressed under the coracoacromial arch. Muscle tension itself can restrict circulation when the tendon's supply of arterial blood runs through the contracted muscle [22].

In de Quervain's syndrome, the retinaculum hypertrophies and traps the abductor pollicis longus and the extensor pollicis brevis in a narrowed first dorsal extensor compartment. Tendons and ligaments also undergo significant modification when they turn corners or insert into bone. The tendon matrix changes its microstructure in response to mechanical forces. Experimental studies suggest that mechanical loading and stresses can induce tissue injury and microstructural changes.

While working at a computer keyboard, the intrinsic and extrinsic muscles of the hand and forearm are moving and contracting dynamically, while the wrist, elbow, shoulder, and neck are in a static posture to support the moving joints. Although static loading of the

trapezius reaches only 30% of maximal contraction, over long periods sustained contraction will result in fatigue. Microtears eventually develop in the affected muscles and tendons. Attempts at healing can be slowed down by repeated injury, with failed healing response, degeneration, and chronic pain. In computer users, the tendons of the wrist and fingers are subjected to traction and shear, according to the degree of muscle contraction, the velocity of tendon movement, and the friction between the tendons and adjacent retinacular tissues. After 500 submaximal work cycles in the wrist, the elastic strain on a tendon was equivalent to what would be accomplished by an 80% increase in load [19]. There is a fibrous thickening in the tendon sheaths and tenosynovium and an attempt repair with an aborted inflammatory reaction in the tendons themselves. Blood flow to the tendons is diminished, and intratendinous fatty degeneration occurs in the tendons. There is no vigorous inflammatory response because there has been no acute injury.

Work-Relatedness of Repetitive Strain Injury

At the center of the controversy around passage of the OSHA ergonomic initiative is whether the perceived explosion of the incidence of RSI is truly due to workplace conditions or to a multiplicity of other factors. In July 1997, the National Institute for Occupational Safety and Health published a monograph entitled "Musculoskeletal Disorders and Workplace Factors." This epidemiological meta-analysis examined the results of over 600 studies focusing on disorders of the neck and upper extremity, including tension neck syndrome, shoulder tendinopathy, tennis and golfer's elbow, hand and wrist tendinopathy, carpal tunnel syndrome, and vibration hand syndrome. The review focused on epidemiological studies based on recognized symptoms and standard methods of clinical evaluation. Studies that included measurement of psychosocial factors were included. The framework for evaluating causality was based on strength of association, consistency of the data, the dose-response relationship for exposure to a given hazard, and the coherence of the evidence.

This meta-analysis concluded that, for neck and shoulder pain and tendinopathy, there was evidence of work-relatedness and causality with a positive relationship among repetition, force, and symptoms. When posture was considered alone, a strong relationship was noted. For elbow tendinopathy, only high force was associated with symptoms repetition, and posture played a much lesser role. For hand and wrist tendinopathy, repetition, high force, and wrist posture play a role in the development of symptoms. But, when these factors are taken in combination, the association is strong. These consistently positive findings from this large sample provide strong evidence of work-relatedness. There are two fundamental weaknesses in this study. 1) There is no clear-cut evidence of a pure dose-response relationship of exposure and the development of symptoms, and there is, to date, no known minimum acceptable "dose" of a given occupational ergonomic hazard much as is seen with chemical hazards. 2) In all these workers, one cannot know for sure whether the ergonomic hazards described in the studies were the only hazards faced, or whether there were a myriad of unforeseen conditions or circumstances that may have contributed. These may include work performed at home or on another job by the worker. However, these studies are useful in that broad impressions can be formulated.

Clinical Evaluation

The first step in developing a treatment plan is deciding whether the problem is indeed a manifestation of cumulative trauma or of other underlying pathology, such as an autoimmune or metabolic disease that affects nerves, tendons, or muscle. The clinician must also decide whether the disorder is work-caused or simply work-aggravated. To simply to call something "work-related" is insufficient. Although some RSIs are highly localized with a straightforward method of treatment, others may be poorly localized and present in an inconsistent and sporadic manner. A detailed medical and occupational history helps identify possible work-related risk factors. It is necessary to ascertain whether the risk factors have sufficient duration to cause or aggravate the problem and to find an association between the workplace and the onset of the symptoms. It may be impossible to tell whether the patient was asymptomatic before beginning the position. Because of the wide publicity given, RSI patients may have learned their presenting manifestations and may use their knowledge for secondary gains. It is important to get a sense of the social dynamics at the workplace. This may take several patient visits, and may even necessitate visiting the workplace. Social issues frequently confound the problem. Employees in a stressful or boring work environment may seek medical attention with an unstated goal of being transferred to another position, being removed from work, or being guaranteed continued medical coverage. The patient may have already had an evaluation by a physician employed by the workers' compensation insurance company, and therefore not objective.

Musculoskeletal disorders signs include decreased range of motion, limb deformity, decreased grip strength, and loss of function. Musculoskeletal disorders symptoms generally include numbness, burning, pain, tingling, cramping, and stiffness. These can appear gradually as

muscle fatigue and pain at work and disappear at rest, but become more severe with increased exposure and continue after work. Symptoms may be localized or diffuse. Over time, symptoms become continuous and spread up the arm to the shoulder and the neck. In a typical case, an employee visits the company nurse and complains of musculoskeletal symptoms. The nurse refers the worker to the company physician, who advises the patient to take time off, wear a wrist splint, and take anti-inflammatory medication. When the employee returns to work, the symptoms return. The employee is referred to a specialist. Additional conservative measures follow. All too frequently, the patient ends up in the operating room. There is initial symptom relief, and the patient returns to light duty, then regular duty, and the symptoms recur. The worker is then viewed as a high-risk workers' compensation case, and some cause is found for laying the patient off. If the compensation claim is denied, an attorney becomes involved, and there is a court hearing. A rehabilitation nurse for the insurance company steps in for a permanent disability rating, and a second medical opinion is sought for a permanent disability payoff, which may take years. The process may literally consume the patient's life. There is a loss of self-esteem and income, causing home strife and depression. Patients see themselves as unemployable and end up as the taxpayers' burden. The longer the patient is out of work, the less the probability that the patient will ever get back.

Because the workers' compensation system was designed to deal with acute injuries, employers and workers' compensation carriers have great difficulty in dealing with workers suffering from RSI. An acute injury has a definite time of onset, an identifiable cause, a clear-cut plan for treatment, and a clearly defined time when the worker should be able to return to work. Workers with RSI pain have none of these conditions. The perception of malingering and secondary gain pervades. As productivity declines, the worker is laid off. Employers are unwilling to make accommodations, and will not allow return to work until the employee is 100% fit. Unions often get involved, OSHA investigates, litigation follows, and the costs of treatment escalate.

This scenario is played out tens of thousands of times across the United States on a yearly basis. This reflects the haphazard and reactive way in which RSI is typically treated. It has recently been realized that only with a proactive approach that begins in the workplace is this problem going to be addressed. Only then will significant inroads be made in reducing the national incidence of WMSDS.

A coordinated multidisciplinary approach is necessary. It involves workers and management working with occupational physicians, ergonomic engineers, industrial psychologists, and employee team coordinators. There needs to be a closer working relationship between industry and medicine. By employing ergonomics, work environments will be configured to fit employees' physical capabilities and reduce those hazards that rob employees and industries of their productivity.

For musculoskeletal disorders management, one requires a prompt response to musculoskeletal disorders when they occur. Employers need to determine the need for work restrictions. Employers must provide access to health care professionals, provide the health care professional with occupational information, and obtain written options from the heath care professional. This information includes description of musculoskeletal hazards, available work restrictions, and opportunity for heath care professionals to do a workplace walk-through. The program must be evaluated, and records must be kept. There is also increasing difficulty in performing the job. A musculoskeletal disorders symptom becomes significant when a health care professional is needed or if there is one or more days off of work, or there is a necessity for restricted work activity or transfer or retraining to another job.

The Necessity for an Ergonomic Program

People work best and more productively and safely in a proper physical environment. People have attempted to adapt to a fixed work environment, but these have resulted in the development of musculoskeletal disorders. Ergonomic designs change the workplace physical environment, the size and arrangement of workspaces, the physical demands of manual tasks involving the upper extremity, and the design of hand tools. The fundamental goal of ergonomic designs is to improve people's ability to produce and to work, reduce lost work time, and thereby lower work error or accident, which would decrease productivity. Studying the human and machine interface is the essence of ergonomic redesign. Ergonomics is an applied science that coordinates the physical features, devices, and working conditions within a selected job along with the capacities of the people working within that environment. When a new production process or equipment change is being considered, the following needs to be taken into account: The working heights, the reaches, the distances one must reach, the necessity to move, to push, to pull, and to lift while standing or sitting, the weights of the materials an employee must move horizontally or vertically during the given operation, the hand motions needed to grasp or pinch materials, the tools used for each process, and other physical capabilities required by the arm and hand. In addition, the path of workflow during manual handling of materials is critical, as are the required speed and frequency of manual activities that are demanded of an employee. Locating work surfaces, tools, and raw materials in awkward reaches causes the individual to adopt

body postures that can overstress the neck, shoulders, elbows, wrists, and hands.

Reaching for products requires the shoulder to be used. Shoulders tend to fatigue when the employee raises the arms above shoulder height or behind the neck. The supraspinatus muscle accomplishes abduction of the glenohumeral joint in the shoulder. The supraspinatus tendon also functions as a humeral head depressor, thus widening the subacromial space between the rotator cuff tendons and the overarching acromion. With heavy, repetitive overuse in shoulder abduction, overhead lifting, or prolonged forward flexion, the rotator cuff tendon becomes worn and allows the humerus to ride upward under the acromion, creating an impingement lesion with pain with shoulder abduction as the humeral head impinges on the lateral aspect of the acromion, further entrapping the supraspinatus tendon, with wear on the supraspinatus tendon and in the subacromial bursa, with subsequent inflammation and pain. If the arm is held elevated, shoulder muscle fatigue and biceps tendinopathy result [23].

This has been identified as a major concern in the workplace, especially for older workers who have reduced joint mobility. Sustained elevated arm work, especially supporting a load, must be minimized to avoid shoulder muscle and tendon fatigue and tendinopathy. Fatigue and tendinopathy will develop if the relative load of the muscles is over 40% of the maximum voluntary contraction, and the rest periods between contractions are shorter than 10 times the contractile period. Short duty cycles, less than twenty per minute, with low loads less than 0.4 kg, with no more than 35 degrees above shoulder level are acceptable, provided that work activity is not maintained for long periods [24]. Even without a hand load, any elevation of the arm in abduction or forward flexion above 90 degrees greatly increases the stress on the rotator cuff. Acute tendinopathy of the shoulder can be induced by high-velocity arm movements such as tossing materials. Such motions can result in sudden and excessive strain on specific tendons as particular muscles contract to provide the acceleration and deceleration necessary to execute gross motion while maintaining joint integrity. When reaching forward, the shoulder joint is flexed and the elbow becomes extended. If a load is held in the hands, the load moments at the elbow and the shoulder can become large relative to the flexor tendon moments required at both joints. Thus, even small loads cannot be supported for sustained periods, especially if the arm or forearm is elevated and pushed forward. Thus, power tools used during a workday for sustained periods should be suspended from an overhead tool balancer designed to minimize the weight effect. Also, workpieces or assembly should not have to be supported by one hand while the other one performs the required operation. Good workplace design provides adjustable fixtures that support the workpiece in proper orientation for the operator, taking into account both visual and manual task requirements.

The shoulder is assisted by the posture and motion of the elbow. When the elbow is bent, it assists in shoulder flexion motions during manual handling of products. In addition, the elbow assists in bringing the hand to the face. Epicondylitis of the elbow (lateral most common) has been reported with constant use of a hammer, repeated supination or pronation, repeated forceful wrist extension, and supination of the gripping hand with wrist extension [25].

Additionally, forearm postures are not only dictated by the location of the hand, but also by hand orientation around the longitudinal axis of the forearm. If the hand is supinated, then the arm will be adducted and close to the torso. If the task requires the hand to be pronated, then the arm will be more abducted and elevated. If the hand is located in a position that already requires the arm to be elevated, then using the prone hand posture will further require arm elevation. If a screw must be turned in a clockwise direction, with supination of the forearm, it is important that the elbow be flexed to 90 degrees, running good mechanical advantage for the biceps brachii. If the elbow is extended, the short forearm supinators, which fatigue much more easily than the biceps brachii, accomplish supination. The mechanical advantage of the biceps disappears with elbow extension [26]. When attempting to push or pull with one hand while sitting, the resulting strength exerted depends on shoulder and elbow angles. When the elbow is straight or locked in extension, push and pull forces can become quite high. As a general rule, each employee should have the elbows postured at midrange, at 90 degrees of flexion. When keeping the elbows close to the body, at no further than 30 degrees of shoulder abduction, and working within arm's length, one must minimize forearm rotation and maintain a pistol grip so that hand strength is maximized [27].

Cumulative trauma to tendons, tenosynovitis, tendinopathy, de Quervain's syndrome, and paratendinopathy can occur as a result of repetitive motion about the wrist. Awkward posturing exacerbates this. Examples of this include ulnar deviation of the wrist with a fixed thumb, rapid finger flexion, grasping in radial deviation, violent pulling, wrenching grip, twisting with forearm pronation and supination, or pinch followed by quick pronation. Excessive flexion and extension of the digits against resistance, and overuse of index finger with pistol-type air tools can cause trigger finger.

Force

The force with which an employee must lift a grip is associated with cumulative prominent disorders of the upper

extremity. The greater the force exerted, the greater the potential for these disorders. External loads on the musculoskeletal system induce high muscle, tendon, and joint forces. Because these activities are under precise motor control during work, peak tissue stress is usually well within the physiologic capacity of the tissues, provided that the forces are of short duration and rest periods are adequate. Overexertion or very frequent exertions can result in diminished functional capacity. This can cause in the tendon a reaction to a mechanical strain of the tissues when there is not adequate rest to allow physiologic recovery and adaptation [28]. With further exertion, tendon collagen fibers become separated. At the point of greatest stress where tendons pass around adjacent bone or ligament structures, the collagen fibers can be shredded, leaving debris-containing calcium salts. These calcium salts and circulatory fluids within injured tendons produce further swelling and pain [29]. If the harmful work activity is continued, degeneration will involve surrounding tendon synovia and bursae. This is particularly present when the weight of the object being held or lifted is substantial. Other factors, such as the shape and configuration of objects may make lifting difficult as may poorly fitting gloves [30].

In the workplace, force can be reduced by adding a better gripping surface such as rubber slips to tool handles, reducing the weight held by workers through the use of gigs or balancers to keep hand forces to the minimum, aligning the object's center of gravity to the hand and body center of gravity, reducing rotating movements caused either by the tool or work design, and reducing tool power speeds and torque.

Repetition

Repetitiveness is often cited as a risk factor for cumulative trauma disorder of the upper limbs [40]. Although the relationship between this exposure factor and cumulative trauma disorders has been established, the acceptable dose-relationship or tolerance ratios have not. Engineers and managers use the term repetition to indicate task cycles and standard task completion times. Other factors such as selected job methods or length of time spent on a given task will vary the repetitiveness of the job.

Workplace Controls (Modifying the Workplace to Prevent Tendinopathy)

To control repetitiveness, an administrative control is recommended. Such controls include job method change, relief of workers, job enhancements, and change of production pace. Sometimes engineering controls will create less manual work for employees and reduce the repetitiveness of job tasks. Examples of workplace controls include reducing the weight of objects handled, rotating the job functions, varying the job tasks, allowing short breaks, using sit/stand workstations, using antifatigue mats, providing footrests, and providing cushion insoles. In such a way, static postures can be alleviated. To relieve excessive force, one uses balanced power tools and provides lift assists. For sitting for an extended period of time, one implements standing breaks, lumbar supports, appropriate seats with padding on the seat with good lumbar support, and seat height adjustments that are correct.

- For workstation or edges that press hard into muscles or tendons, one has to provide round edges and large handles, and pad the surfaces of handles.
- For using hands or body as a clamp to hold objects while performing tasks, one implements fixture, clasps and jigs, uses job rotation, and pads work surfaces.
- For objects that are too heavy, one needs to lighten the load, use lift assists, use lift tables, and allow two people to lift as a team.
- For horizontal and vertical reaches that are too long or too high or low, one needs to readjust the workstation so these problems are alleviated.
- For tasks that involve moving objects significant distances, one needs to use mechanical conveyors, such as forklifts, hand dollies, and carts. For conveyor belts, objects should have appropriate handles to make things easier to lift without assuming awkward positions or high contact stresses.

A simple reach triggers a complex action of the arm and hand. The type of motion, the amount of motion, and the duration of the motion determine the level of body stress. Reducing stress requires proper position of the body parts. Work surfaces and seats must be adjustable in heights and reaches. Proper positioning is tied closely to the measurement of body size and anthropometry. Through anthropometry, proper positioning is often achieved. However, this alone will not eliminate ergonomic posture stresses if work motions or applied force are needed to complete a job.

Hand Tool Shape and Size Considerations

Many of these workplace hazards are directly related to the design of hand tools and the methods employed when using these tools. As forceful hand grip relies on muscle contractions of the forearm, with force being transferred to the bones and the joints of the fingers via the long flexor and extensor tendons, the level of muscle and tendon exertion largely depends on grip configuration and, to a lesser extent, on hand and wrist anthropometry. Furthermore, biomechanical studies disclose that the angle of the wrist directly affects grip strength. It is pro-

posed that the wrist be kept relatively straight during forceful gripping to avoid wrist strain [31]. Failure to do so can result in tendinopathy and synovitis, with later entrapment of the median nerve within the carpal tunnel. Thus, the shape and size of a hand tool can have a direct effect on the worker's performance ability, grip strength, and arm comfort.

Tool Shape to Avoid Wrist Tendinopathy

Allowing the hand and wrist to remain in alignment during forceful grip exertions necessitates specific tool handle configurations. For example:

Cylindrical Versus Pistol-Shaped Tools

Based on biomechanical considerations, the handles of powered drivers such as drills should sometimes be pistol-gripped when drilling into a vertical surface. Some horizontal surfaces that are low down can be drilled with pistol-grip tools as well, while other surfaces higher up require a cylindrical grip. Usually, the driving torque of a tool creates the tendency for the tool to rotate in the worker's hand unless firmly gripped. Generated forces near maximal strength are not uncommon in such activities. If the wrist is forced into deviation during such exertions, there is an increased risk of cumulative trauma [32]. Occasionally, the cylindrical grip tool may need to be suspended from a balance beam in the ceiling.

Bent-Pliers Design

In a comparative study between two different types of pliers used by 80 employees, over 60% of those using the common straight-handled pliers developed wrist and related disorders at the end of 12 weeks, while only 10% of those using the new bent-handled design were affected [33].

Bent-Knife Handle Design

In a similar situation, in poultry processing operations, with a common straight-handled knife that required extreme wrist flexion and ulnar deviation, the cumulative trauma incidence rate was 17 per 100 workers a year, 50% higher than the plant average. A pistol-grip-handled knife reduced the need to continually grip because knives sometimes get slippery between cuts. By relaxing the hand between cuts, muscle fatigue incidents were reduced [34].

Bent-Hammer Handle Design

The curve in the handle has resulted in less muscle fatigue as measured by decreased grip strength than was the case when using a straight-handled hammer to pound 20 nails. The optimum curvature is believed to be between 5 and 10 degrees [35].

Tool Shape to Avoid Shoulder Abduction

If the shape of a tool requires extreme wrist deviation, a person will often raise the arm to reduce the stress on the wrist. A small amount of arm abduction at the shoulder up to 20 degrees from the vertical will not normally create an excessive load moment on the shoulder. Greater abduction, however, rapidly increased shoulder load moment. If a heavy tool is involved, abduction of the arm simply compounds the moment requirement of the shoulder, since its weight acts at the end of the upper extremity. In general, if shoulder abduction angle was about 30 degrees, the time to reach significant muscle fatigue was over 3 times than when abducted 60 degrees, and 6 times than when at 90 degrees of abduction. Bending tools such as a soldering iron can and will reduce the requirement for wrist ulnar deviation and shoulder abduction [36].

Tool Shape to Assist Grip

Any tool that may require a person to exert a pushing or pulling force across the palm should be designed with a flared handle, which will guard against the hand slipping. The use of long-padded handles distributes the force on the fingers and palmar tissue, avoiding stress concentrations in sensitive areas. In general, any tool that must be squeezed forcibly should be designed with handles that avoid concentrating grip forces in the center of the palm, as it is poorly designed to withstand direct force application due to the presence of the median nerve, radial and ulnar arteries, and finger flexor tendon synovium in this location. The length of a tool handle should be sufficient to distribute compressive forces across the palm and across all the digits. The force area must be at least 9 cm long to assure that handles are supported on both the thenar and hypothenar muscles [37]. Reverse curvature on pliers and shears reduces the forces across the palm. The compressive forces acting across the palm are significantly higher with triangular or rectangular-shaped handles than with circular or square handles. Pulling a handle toward the body, a T-shaped handle is superior to a straight cylinder. When low continuous torque is required, a cylinder that could be grasped easily is preferred to other shapes [38].

Size of a Tool Handle to Facilitate Grip

Upper strength and resulting stress on finger flexor tendons vary with the size of the object being grasped. If the handle force is applied to the distal segment of the

fingers, as is the case when grasping a large tool, the counterforces can be 2 to 3 times higher than when a comparable force is applied to more proximal finger segments [39]. Conversely, if an object is very small, the fingers cannot effectively apply force to it, partially because finger flexor tendons become extremely shortened. This is especially true when attempting to forcibly grasp a small object or tool handle with a flexed wrist, as this action further shortens the finger flexor muscles. Maximum grip strength is achieved when the handle begins to close for about 8 cm. In general, women demonstrate approximately half the grip strength of men. When grip strength exceeds 40 Newtons and is repeated often, the odds of developing carpal tunnel syndrome are 15 times higher than if workers exerted less than 10 Newtons infrequently [40]. Thus, force and magnitude grip frequency play a role in the development of RSI.

Employee Exercise Programs

RSIs occur more frequently in people who do not follow a regular exercise program. Looking at the computer workplace, mini exercise breaks throughout the workday not only diminish the incidence of RSI but actually increase worker productivity and prevent productivity "drop-off" that frequently occurs at the end of the day [41]. There are many published "mini break" exercise programs that allow workers to stretch the neck, shoulders, forearms, hand, and wrists at the workstation. There are also "maxi break" exercises that workers can do twice daily [41]. Other options include job rotation, introduction of other tasks into the work cycle, and limitation of work hours. Many companies have included in-house fitness facilities where stretching, relaxation, and strengthening exercises are taught. Pictorial handouts and poster displays throughout the workplace may also be useful. Many software companies have developed exercise programs that flash reminders on the screen that instruct the worker to stop work, and start exercise.

Efficacy of Ergonomic Programs

OSHA's estimate of the overall effectiveness of ergonomic programs is expressed in the mean reduction of musculoskeletal disease injury rates for all musculoskeletal disorders. OSHA's case study reported at a meeting 96% reduction in injury rates. The median and mean reduction of the lost workdays was 82%. Although the effectiveness of individual ergonomic programs can vary, most interventions achieved at least a 30% reduction in injury rates [42]. Also, 70% of the case studies reduced musculoskeletal disease rates by half [43]. A quantitative study found a statistically significant higher number of back injuries than would be expected in manual handling jobs that required an exertion beyond the physical capabilities of more than 25% of the working population [44]. Back injuries could be reduced by 66% in jobs with a level of physical exertion such that 75% or more of the working population can perform it without overexertion [44].

For jobs that involve exposure to multiple risk factors, the risk of work-related musculoskeletal disorders can be reduced by either reducing or eliminating exposure to one of the aforementioned risk factors or reducing duration of exposure to the risk factors. Armstrong and Silverstein examined the prevalence of carpal tunnel syndrome and tendinopathy among populations exposed to various combinations of risk factors, including low force–low repetition, high force-low repetition, low force–high repetition, and high force–high repetition [39]. The high force and high repetition population was exposed to 2 or more risk factors, and the prevalence of carpal tunnel was statistically significantly elevated among workers exposed to high repetition alone, or to both risk factors. Odds ratios for hand and wrist tendinopathy were elevated for all 3 groups of exposed workers, but were statistically significant only among workers exposed to both high force and high repetition [41]. Based on implementing ergonomic conditions that reduce employee exposures from 2 risk factors to one, a reduction of injuries of 83% for carpal tunnel syndrome and 89% for tendinitis could be expected. Punnet, in a cross-sectional study in an automobile stamping plant, assessed exposures to workplace risk factors that reflected intensity and duration of exposures to any of several risk factors, and he found a positive, statistically significant relationship between risk factor exposure and prevalence of upper extremity disorders [45]. Data from this study indicate that the prevalence of employee-reported symptoms of upper extremity disorders and the prevalence of physician-confirmed musculoskeletal disease could be reduced more than 50% if the exposure was reduced by at least half [45]. The median estimated effectiveness of ergonomic programs and interventions ranges from about 28% to 43% in multiple OSHA studies. If all work-related risk factors were eliminated, the median effectiveness would range from 56% to 86% [46]. Overall, OSHA believes that the incidence of musculoskeletal disorders would be reduced by a half or two-thirds as a result of implementing ergonomic programs. These risk factors include forceful lifting, pushing, pulling, repeated bending, twisting, repetitive arm or hand motions, static and awkward postures, contact stresses, and whole-body and localized vibration.

OSHA's evidence consists of 92 case studies that document reductions in musculoskeletal injury rates that have resulted after ergonomic programs and employers have implemented interventions. Several epidemiology

studies have shown quantitative relationships between the intensity of duration of exposure to workplace risk factors and the risk of musculoskeletal diseases. This provides direct evidence that reducing exposures will reduce musculoskeletal disease incidence [48]. From these studies, OSHA estimates that ergonomic programs and interventions will reduce the incidence of musculoskeletal disorders and lost workdays by a mean of 76%.

Tadano demonstrated a dramatic decrease in the incidence of repetitive strain injury in a company that used only employee monitoring and job rotation [47]. Schierhout and coworkers also showed a reduction in RSIs simply with surveillance and ergonomic education [48]. Schneider showed that, when one insurance company with 800 workers improved its workstation design, it decreased absenteeism from 4.4% to 1.6%, increased efficiency in processing claims by 137%, and saw a 9% decrease in errors [49].

Controversies

There is still international controversy about the true nature of RSIs and whether they should be considered work-related. This is due in part to the lack of outcome-based prospective controlled studies to determine treatment effectiveness. There is no defined "dose" of ergonomic hazard that can be determined to cause RSI in a given population. Several states (notably Virginia) have followed the Australian model, which claims that RSI is not work-related, and that it might not even have an organic basis at all [50]. In Australia, workers with RSI do not receive workers' compensation benefits. This presupposes that this condition is purely psychosocial. That view is supported by the fact that many clinical presentations of RSI have no neurological or physical findings, although the patients complain of pain, numbness, or weakness. Objective tests are often negative as well. The lack of definitive findings may be due in part to the lack of definitive tools to make the diagnosis objectively. RSI often occurs in workers with low pain tolerance who work in repetitive, monotonous jobs, and have many personal problems unrelated to their occupation [51]. Although this may be true for some patients, there is no scientific evidence to date to suggest that this is true in the majority of patients.

Repetitive strain injury is a broad, multifaceted condition. Sweeping it under the legislative carpet will not lower the incidence of employee pain or increase worker productivity. It will merely silence the complaints or shift medical coverage for the problems to the private sector. These problems must be addressed directly and primarily in the workplace rather than in the clinic. Through prevention, the biggest impact of intervention will be felt.

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12
Rotator Cuff Tendinopathy

Andrew Carr and Paul Harvie

Introduction

Shoulder pain is common: 16% of the general population suffer from it [1]. Rotator cuff disease is the commonest cause of shoulder pain, forming a large proportion of the workload of the specialist shoulder surgeon (of 1500 new shoulder referrals to a UK shoulder surgeon, 310 had rotator cuff tears) [2]. The morbidity associated with rotator cuff disease in terms of pain and loss of function is variable, but can be severely debilitating. In parallel with this, there is the cost to society in terms of loss of employment, Social Security claims, and the utilization of medical resources. Controversy exists in almost every area of the subject, and this chapter gives a broad overview of rotator cuff disease.

Basic Science of the Rotator Cuff

The rotator or musculotendinous cuff is a complex of 4 muscles that arise from the scapula. As these muscle and tendons extend toward the humerus, they intersect and blend with adjacent tendons and the subjacent capsule, forming a continuous cuff around the humeral head (see Figure 12-1). This cuff has a central role in the mechanics and function of the shoulder. The rotator cuff, however, does not function alone: it is part of a complex system of muscles, ligaments, and joints that affect shoulder movement.

The mechanics of cuff action are complex, but may be thought of as having 3 main functions. They rotate the humerus with respect to the scapula; they compress the head into the glenoid fossa, providing dynamic stability, particularly in the midrange of motion; and they provide muscular balance counteracting unwanted force components produced by non–rotator cuff muscles, e.g. deltoid or latissimus dorsi. Kuhn et al. give an excellent summary of the biomechanics of glenohumeral stability and shoulder kinematics [3].

The principal muscles involved in forming the rotator cuff are the supraspinatus, infraspinatus, subscapularis, and teres minor, although the long head of the biceps should also be considered as a functional part of the cuff [4]. From the suprascapular fossa, the supraspinatus passes laterally coursing beneath the coracoacromial arch and inserts into the greater tuberosity of the humerus. The space defined by the acromion posterosuperiorly, the humeral head inferiorly, the scapular spine posteriorly, and the coracoacromial ligament anterosuperiorly is known as the supraspinatus outlet. The supraspinatus tendon must pass through this outlet to its insertion, and here it can be compressed between the unyielding humeral head and the coracoacromial arch.

Near its insertion, fibers from the supraspinatus tendon fuse posteriorly with fibers from the infraspinatus, while others extend anteriorly toward the rotator interval, the space between the anterior portion of the supraspinatus and the superior portion of the subscapularis. Medially, the coracoid projects through the rotator interval, and the tendon from the long head of the biceps passes via the interval to its glenoid attachment, ensheathed in fibers from the subscapularis and supraspinatus tendons. Fibers of the coracoacromial ligament extend from the coracoid to the rotator interval and the supraspinatus, contributing to the cuff-capsule complex. Muscle contraction can thus tension the cuff and capsule in addition to applying force to the greater tuberosity.

The infraspinatus arises from the infraspinatus fossa of the scapula and inserts into the greater tuberosity posterior to the supraspinatus. Near its insertion some fibers diverge to blend with the supraspinatus anteriorly and the teres minor inferiorly. The infraspinatus can therefore tension the entire posterosuperior cuff capsule complex.

The subscapularis is the most powerful of the cuff muscles. Originating from the subscapular fossa of the scapula, it inserts onto the lesser tuberosity and has widespread attachment to both capsule and glenohumeral ligaments.

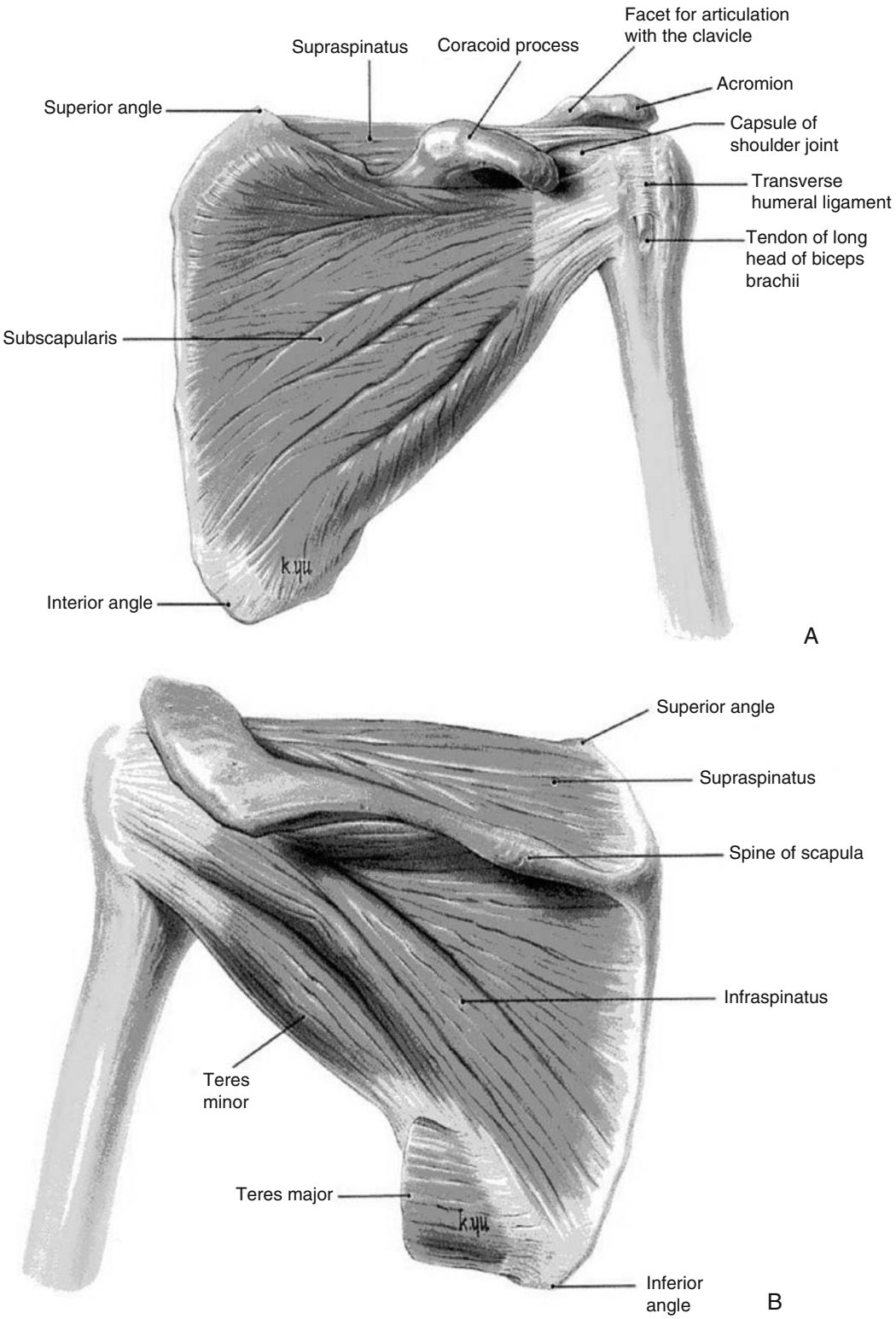

Figure 12-1. Gross anatomy of the shoulder.

Teres minor is the smallest of the cuff muscles. Originating from the lower lateral scapular border, it inserts inferiorly on the greater tuberosity.

At the insertion of the tendon fibers, a 5-layered structure of the cuff-capsule complex has been described [4]. The transverse transmission of force across the rotator cuff has been explained in terms of this structure and may be important in the initiation of cuff tears as significant shear forces occur.

The blood supply of rotator cuff structures is also important. Supraspinatus receives its blood supply primarily from the suprascapular artery, but contributions from both anterior and posterior circumflex humeral arteries and the subscapular artery have been reported. Classically, Codman [5] identified a "critical zone" at the supraspinatus tendon insertion as a region that had inadequate blood supply. More recently, a differential circulation between articular and bursal-sided tendon tissues has been reported, with the bursal side having better perfusion with respect to its articular side [2]. Despite this, laser Doppler studies have demonstrated a normal vascular supply with many anastomoses around this "critical zone" in uninjured cuff tendons, and impaired blood supply may be a secondary event in cuff tear pathogenesis.

Classification and Incidence of Rotator Cuff Tears

Rotator cuff tears are common and typically involve the supraspinatus tendon and often the posterior cuff to a variable degree. Subscapularis involvement may be present, and is easily overlooked.

Tears about the rotator interval are less common, and identification can be difficult. Tears may be vertical, horizontal or combined with widespread differences in size and degree of retraction.

There is no universally accepted classification of rotator cuff disease. However, important variables to consider when describing rotator cuff lesions include duration, depth, and size, as well as condition of the muscle and tendon. Acute tears may be associated with a traumatic event resulting in pain and dysfunction. Chronic tears may be associated with a variable degree of pain and weakness. Occasionally an acute extension of a chronic tear can follow shoulder trauma.

The depth of the tear will differentiate partial- from full-thickness tears. Partial tears can occur on the articular or bursal side of the tendon or within its substance. Classification of partial tears has been reported, but it is difficult to apply and not widely used. More concordance exists with the classification of full-thickness tears. Typically, they are described as small (less than 1 cm in diameter), medium (1 to 3 cm), large (3 to 5 cm), or massive (larger than 5 cm).

The true incidence of rotator cuff tears is unknown. By definition, such an incidence would refer to the occurrence of new rotator cuff tears. However, as individuals may remain asymptomatic, the actual incidence in a given population is impossible to measure, as only symptomatic individuals will present to the shoulder surgeon. The "true" prevalence of rotator cuff tears has been widely reported, and results vary depending on the design of the study. Cadaveric studies have shown prevalences between 5% and 30%, but these are age dependent. The Lehmans [6] study of 235 cadavers found the prevalence of full-thickness tears to be 17%. The mean age of those with tears was 77.8 years, compared with 64.7 years in those without.

In contrast, in Tempelhof's study of 411 living asymptomatic patients, 13% of patients under 60 years of age and 51% of patients over 80 years of age were diagnosed with cuff tears despite being asymptomatic [7], indicating the importance of age in the prevalence of such lesions.

Partial-thickness tears appear to be about twice as common as full-thickness defects. Bursal-sided lesions are more common, and studies have shown that these can cause more severe symptoms. Furthermore the progression of partial-thickness tears has been demonstrated both in terms of size and development into full-thickness tears. Much of the literature on the prevalence of rotator cuff disease has used cadaveric or symptomatic patients. The very fact that many asymptomatic individuals may have a rotator cuff lesion means that accurate data on the population as a whole are difficult to obtain, and all other data must be interpreted in view of this. Sher et al. [8] used magnetic resonance imaging (MRI) to scan 96 asymptomatic individuals with no history of shoulder complaints or evidence of pathology on clinical examination. For all age groups, the overall prevalence of rotator cuff tears was 34% (14% full-thickness, 20% partial-thickness). In the subgroup of individuals older than 60 years of age, the prevalence increased to 54% (28% full-thickness, 26% partial-thickness), thus showing the potential for normal, painless, functional shoulder activity despite observed rotator cuff abnormalities on MRI.

Etiology and Pathogenesis of Rotator Cuff Disease

The pathology of the rotator cuff includes a broad spectrum of conditions including reversible tendon inflammation, irreversible tendon degeneration, partial-thickness cuff tears, reversible calcific tendinopathy, full-thickness cuff tears, and degenerative glenohumeral arthritis (cuff tear arthropathy associated with chronic, massive cuff tears). The heterogeneity of rotator cuff disease, as well as the notion that the disease may not

represent a continuum of the same process, may explain differing viewpoints regarding its origin [2,7,8].

Postulated mechanisms of rotator cuff injury are either intrinsic or extrinsic. Studies supporting intrinsic mechanisms have included vascular and anatomical studies as well as evaluation of overuse syndromes. The critical zone described previously was thought to represent a region of poor vascularity at risk of injury and with little capacity for repair. Although generally refuted, aging, injury, or external compression may reduce perfusion, resulting in cuff injury. Degenerative changes in the cuff that may precede tearing have been confirmed histologically. These changes may in turn predispose to further injury and or tearing [6].

Normal cuff tendon is composed of collagen and small amounts of elastin, glycosaminoglycans (GAGs), proteoglycans, and water. The collagen present is predominantly Type I (>95%) and forms the main constituent of tendon fibers. Many other types exist but are found in much smaller quantities. Type III collagen is associated with the endotenon, Type IV with basement membranes, and Type VI with cellular interactions, but Types V, XII, and XIV have also been implicated in cuff tear pathogenesis. Under conditions of tendon injury and repair, collagen metabolism is significantly altered. There is an overall reduction in tendon collagen content, but gene expression of collagen Types I, VI, XIV, and particularly Type III, increases, the last thought to play an important role in stabilization of the extracellular matrix. In addition to this, Type II collagen expression is inhibited and mature crosslink formation increases.

Little remodeling is thought to occur before 50 years of age. After this age, remodeling occurs in response to tendon microruptures with the laying down of new collagen fibers that are thought to be of equal quality to preexisting fibers. This is thought to represent the "wear, tear, repair" process of the normal rotator cuff. In chronic tendinopathy, however, remodeling is extensive in an attempt to repair tendon defects. In this case, the previously functional and carefully constructed matrix is replaced by aberrant collagen, which may result in a mechanically less stable tendon predisposing to tearing [9].

The detailed mechanism of collagen fiber remodeling is complex, but is thought to be mediated at the cellular level by matrix metalloproteinases (MMPs) such as collagenases and stromelysins [10]. These zinc-dependent enzymes are capable of degrading all components of the extracellular matrix and are produced as proenzymes by tendon tissues. MMPs in turn are under the control of tissue inhibitors of metalloproteinases (TIMPs).

Other components of the cuff tendons have been seen to be altered in rotator cuff disease. Under normal conditions, the GAG content of supraspinatus is different in comparison to that of biceps tendon and is analogous to that found in fibrocartilage, suggesting an adaptation to mechanical stresses such as compression and shear. GAG deposition increases with both age and in disease states such as chronic tendinopathy [11]. Evidence of further adaptation has been found in diseased supraspinatus tendons by the presence of fibrocartilagenous metaplasia, in keeping with other tendons in the body that are subjected to compressive loads. This functional adaptation may have important consequences for the structural strength of the supraspinatus tendon and an influence on the ability of the tendon to repair after injury.

More recently, the localized deposition of amyloid in tears of the rotator cuff has been reported [12]. Increased sulfated GAGs and Type III collagen content have both been associated with amyloid deposition and, once deposited in tissues, amyloid is resistant to proteolytic degradation. This explains its persistence and continued accumulation leading ultimately to functional and structural failure of the affected tissue. As such, amyloid may play a role in cuff tear pathogenesis.

Calcium crystal deposition is another common finding associated with disease of the rotator cuff. The association between rotator cuff tear arthropathy and the intraarticular presence of basic calcium phosphate crystals (BCP) was identified in 1981 and termed the Milwaukee shoulder [13]. Electron microscopic analysis of synovial tissue from the glenohumeral joints of patients with cuff tear arthropathy revealed microspheroids of BCP crystals, as well as crystals within the synovial fluid. Basic calcium phosphate is a generic term used to describe crystals composed of carbonate-substituted hydroxyapatite, octacalcium phosphate, or rarely tricalcium phosphate. BCP crystal deposition is thought to occur secondarily as a result of severe joint changes associated with massive cuff tears, the crystals further accelerating joint damage by inducing synovial hyperplasia and metalloproteinase production. Calcium crystal deposition is known to occur in other periarthropathies, including calcific tendinopathy and chondrocalcinosis (where calcium pyrophosphate deposition predominates), and often a mixed picture exists in a variety of conditions, such as osteoarthritis.

Although the exact mechanism of calcium crystal deposition is poorly understood, recent studies using mice with the "ank" mutation (ank = progressive ankylosis locus) have increased our knowledge of the mechanism of calcification [14]. The ank mutation causes a generalized progressive form of arthritis accompanied by mineral deposition, osteophyte formation, and joint destruction. The ank gene codes for a multipass transmembrane protein necessary for the transport of inorganic pyrophosphate (PPi) out of cells. PPi is an important inhibitor of calcification, particularly BCP formation. Mutation of the ank gene results in a three- to fivefold decrease in extracellular PPi concentrations, thus producing a milieu conducive to crystal deposition. The

human ank protein is nearly identical to the mouse ank protein, with the human gene mapping to a region on chromosome 5p. Several human pedigrees with joint abnormalities, such as arthritis and chondrocalcinosis, have been mapped to the same locus as the human ank gene [15], although the role of the ank gene in disease of the rotator cuff remains to be seen.

Extrinsic mechanisms popularized by Neer [16] have implicated impingement against the undersurface of the acromion and coracoacromial ligament as primary factors in causing cuff tears. In support of this, it has been found that patients with Type III or hooked acromia have an increased incidence of rotator cuff tears (see Figure 12-2). Changes in the coracoacromial ligament can reduce the supraspinatus outlet area, resulting in extrinsic cuff compression. Distinctive histological changes with shortening and thickening of the coracoacromial ligament have been found in patients with cuff tears. Debate exists as to whether these are primary changes resulting in secondary cuff compression or secondary changes as a result of altered loading after a primary cuff tear. More recent evidence, including pathological changes in the acromion, has suggested that at this site the problem is predominantly intrinsic [17].

Several etiological factors have been associated with the development of rotator cuff disorders. Traumatic events such as anterior glenohumeral dislocation and fracture of the greater tuberosity can result in rotator cuff tears. However, it is difficult to determine whether trauma was the sole cause or whether a preexisting cuff lesion has extended.

Other traumatic insults occur in young athletes such as swimmers or tennis players who participate in repeated overhead activity. Such injuries generally manifest as small partial-thickness tears.

An association between an unfused acromial epiphysis or os acromiale and rotator cuff tears exists and is found in up to 8.2% of patients. Abnormal motion at the synostosis decreases the volume of the subacromial space, resulting in impingement. Congenital subacromial stenosis, a rare abnormality of the subacromial arch, may predispose certain patients to impingement. Attempts to unify intrinsic and extrinsic theories can be made to explain the natural history of rotator cuff tears.

Throughout its life, the cuff is subject to traction, compression, abrasion, inflammation, and, most importantly, age-related degeneration. Lesions of the cuff typically start at the deep surface of the anterior insertion of the supraspinatus near the long head of biceps. Tendon fibers fail when load exceeds their strength—either a few at a time or en masse—and retract after rupture. As a result, the load on remaining fibers is increased, the tendon is detached from bone thus decreasing force generation, blood supply is compromised causing local ischemia, and local tissues are exposed to lytic enzymes from the synovial fluid, which remove any hematoma. Risk from subsequent loading, and in the absence of repair, age-related degenerative processes result in extension to a full-thickness lesion and posterior propagation into the infraspinatus tendon.

With progressive dissolution of the cuff tendon, there is a loss of interposition of soft tissues between the humeral head and undersurface of the acromion, i.e., the "spacer effect" of the supraspinatus tendon is lost, resulting in superior migration of the humeral head and increased load on the biceps tendon. Further propagation of the defect crosses the bicipital groove to the subscapularis tendon, destabilizing the long head tendon.

Pain results in reflex inhibition of muscle action with less effective balance and stability. Increasing superior migration causes wear on the superior glenoid rim and labrum, and abrasion of the humeral articular cartilage on the coracoacromial arch may result in secondary degenerative joint disease known as cuff tear arthropathy. A diagrammatic representation of this "Unifying Continuum Theory" is seen in Figure 12-3.

Despite its attractive appearance, many discontinuities exist in this model, and debate continues as to its applicability. For example, the model cannot explain the variability in progression of partial- to full-thickness tears, the extension of small to large or massive tears, or why only 4% of patients with massive cuff tears develop cuff tear arthropathy. The existence of impingement without cuff tear and vice versa, as well as the heterogeneity of symptoms, simply does not fit into this model.

As a result, a more complex "discontinuous" theory has been developed in which the multifactorial nature of rotator cuff tear aetiology and pathogenesis is recognized (Figure 12-4).

History and Examination

Patient history and clinical examination are key elements in the diagnosis of rotator cuff pathology. Lyons and Tomlinson [18] concluded that preoperative clinical evaluation of a rotator cuff defect had a sensitivity of 91% and specificity of 75%. A detailed history enables the surgeon to perform a "directed" clinical examination, which, if performed correctly, should enable an accurate diagnosis to be made.

History

The overwhelming majority of patients with rotator cuff tears are over 40, the dominant extremity is most frequently affected, and up to 60% of patients can recall an exact incident to which their symptoms are attributed.

Pain, especially with overhead activity, is frequently reported with impingement and rotator cuff tears. Patients may complain of pain at night with the inability to sleep on the affected side, or describe periodic

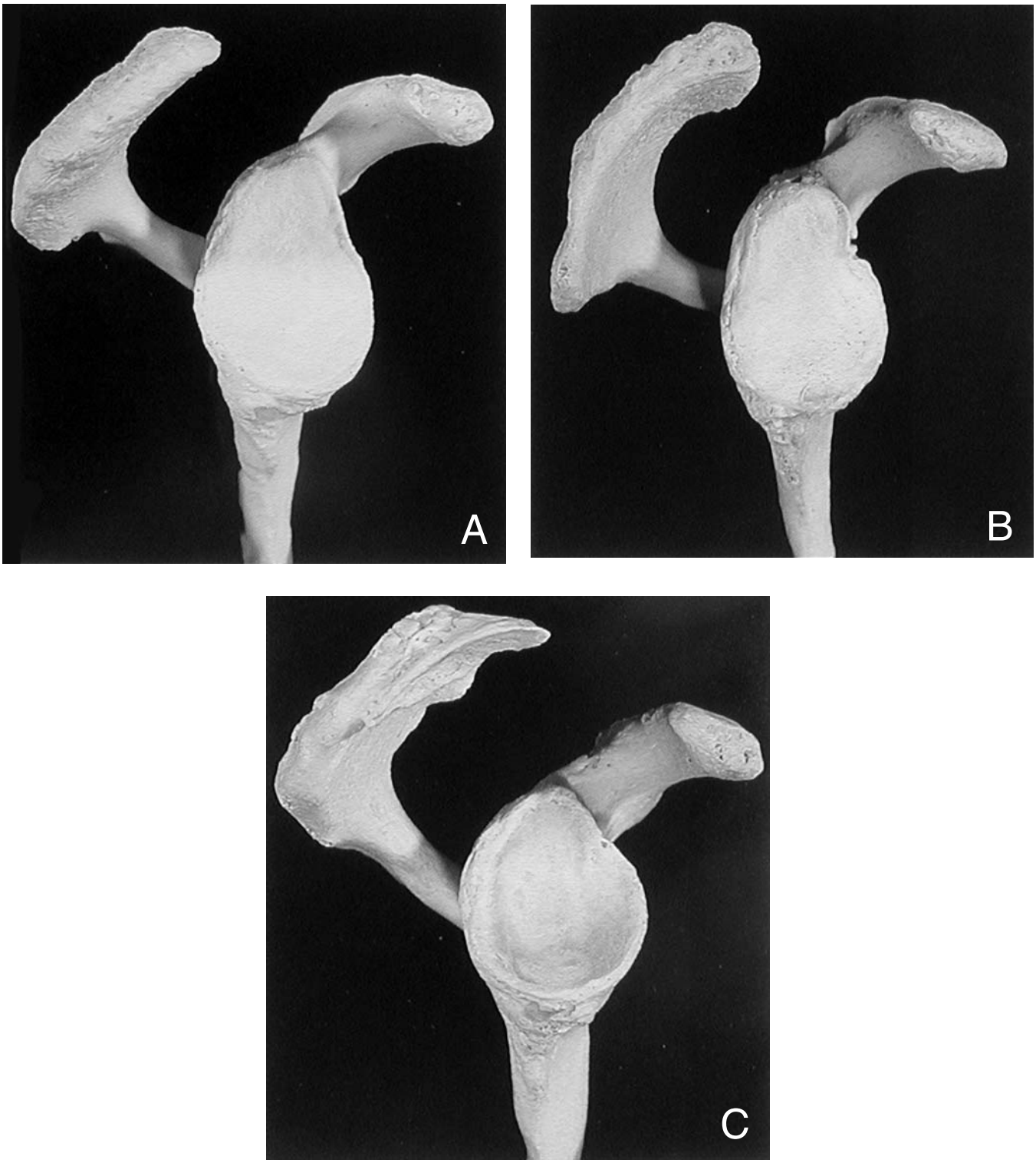

Figure 12-2. Morphology of the acromion. (A) flat, (B) curved, (C) hooked.

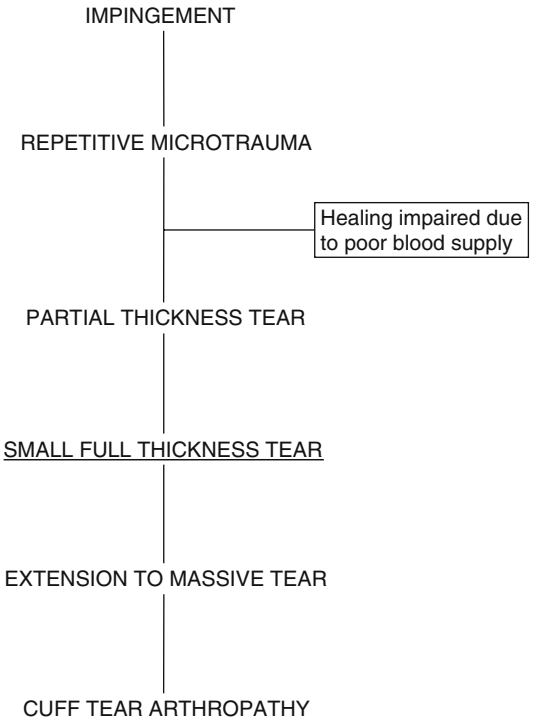

Figure 12-3. Unifying Continuum Theory of cuff tear aetiology and pathogenesis.

exacerbation of shoulder pain wrongly interpreted as "bursitis" or "tendinopathy" as small numbers of rotator cuff tendon fibers intermittently fail.

Weakness of the affected shoulder during abduction and external rotation is another frequent complaint. Full-thickness tears may produce crepitus with the patient complaining of "roughness" in their shoulder movement. Stiffness with reduced range of movement is a variable complaint. Delineating between a true reduction in range of movement and loss of movement secondary to pain can be very difficult.

Despite this, the symptomatology of rotator cuff pathology is extremely variable. Some patients with full-thickness tears have no signs or symptoms and have a normal quality of life, whereas some patients with small cuff tears have pain, marked weakness, and a significantly reduced range of movement. Such variation in symptoms, and more specifically why some patients have pain and some do not, is a question that remains to be answered.

Furthermore, when taking a history it is important to assess what impact a patient's symptoms have on their quality of life. This is vital to establish what priorities and expectations patients have from their treatment and to enable the surgeon to accurately inform the patient whether these results are likely to be achieved.

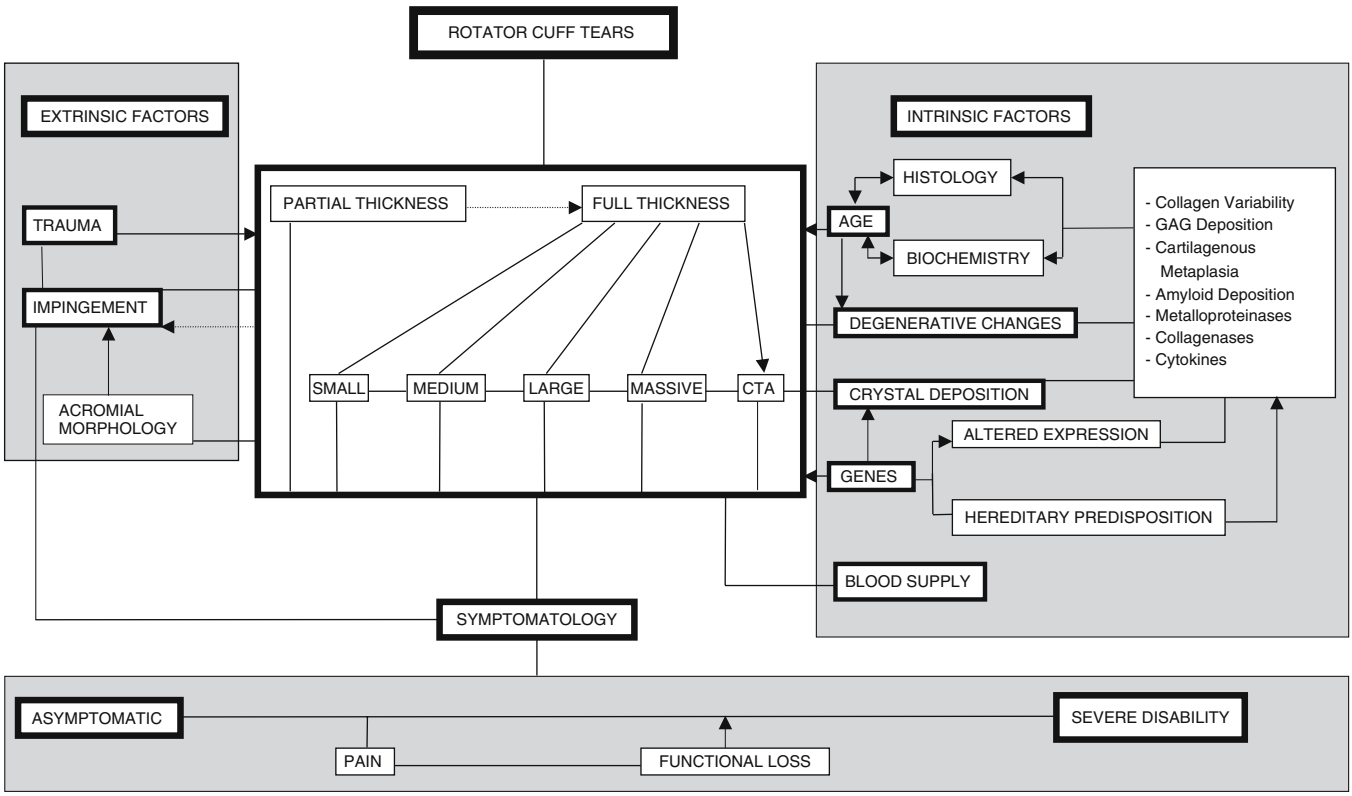

Figure 12-4. Discontinuous Multifactorial Model of cuff tear aetiology and pathogenesis.

Physical Examination

Physical examination can be divided into four parts: general inspection, palpation, range of movement/strength testing, and special tests.

i) Inspection

Inspection begins when meeting the patient. Age, body habitus, use of walking stick, and obvious systemic disease should all be noted. General inspection of the shoulder region may show muscle wasting, deformity or signs of previous surgery. More pertinent to rotator cuff pathology a prominent scapular spine may indicate supraspinatus and/or infraspinatus wasting (Figure 12-5). A ruptured long head of biceps may manifest as an obvious biceps deformity, particularly with elbow flexion.

ii) Palpation

Palpation over the greater tuberosity may elicit tenderness, as may palpation of the bicipital groove when there is associated biceps involvement. As pointed out by Codman [5], defects in the cuff can often be palpated by rotating the proximal humerus under a finger placed at the anterior corner of the acromion. Tenderness around the acromioclavicular joint should be noted, as this may represent degenerative changes in the joint as opposed to rotator cuff pathology.

Figure 12-5. Massive tear of the right rotator cuff with inability to abduct.

iii) Range of Movement/Strength Testing

Both range of movement and strength testing can be carried out simultaneously, and it is currently recommended by the American Shoulder and Elbow Surgeons Society that 4 functionally necessary arcs of motion be recorded: forward flexion, external rotation in neutral position, external rotation at 90 degrees abduction, and internal rotation, with both passive and active ranges of movement being assessed.

iv) Special Tests

Many special clinical tests are recorded in the literature, which attempt to isolate and test specific muscles forming the rotator cuff (including the biceps tendon) and also to elicit signs of impingement. The most commonly used are mentioned below:

Tests of Rotator Cuff Integrity

1. Supraspinatus Test. Described by Jobe, resisted abduction by the arm extended at the elbow, flexed in the scapular plane with maximal internal rotation (thumb pointing to floor). Weakness or pain is specific for a tear of the supraspinatus tendon.

2. Infraspinatus Test. The external rotation lag sign originally described by Hertel [19] involves near maximal passive external rotation with the elbow flexed to 90 degrees. Holding the elbow, the wrist is released. The test is positive if the patient cannot maintain the position and a drop or lag occurs.

3. Subscapularis Test. Gerber's lift-off test involves internally rotating the arm with the forearm/dorsum of hand placed against the "small" of the back. Inability to lift the hand posteriorly off the back or hold the arm in a position just off the back is both sensitive and specific for a subscapularis tendon tear.

No specific test is commonly used to test teres minor. Its function is most commonly assessed by direct palpation of the muscle during external rotation of the arm.

Tests of Biceps Involvement

1. Yergason's Test. First described in 1931, Yergason's test describes pain localized to the bicipital groove when the examiner resists active supination with the elbow

flexed to 90 degrees and the forearm pronated. Yergason thought this pain represented wear and tear of the long head of biceps.

2. Speed's Test. Performed with the shoulder flexed, elbow fully extended, and hand supinated, resistance is applied by the examiner. Pain in the bicipital groove is suggestive of biceps pathology.

Tests of Impingement

1. Painful Arc. With the arm abducted in the coronal plane, pain is experienced typically between 60 and 120 degrees. Pain is often exacerbated by adding resistance.

2. Neer Impingement Sign. This involves forced passive "forward flexion" of the arm. The test is positive if the patient experiences pain with greater than 120 degrees of forward flexion. Neer's test involved a subsequent injection of 5 to 10 mL of 1% lidocaine into the subacromial space. Alleviation of pain on repeating the test confirms impingement.

3. Hawkins' Test. Forced internal rotation of the arm when flexed to 90 degrees.

4. Jobe's Test. Forward flexion to 30 degrees and abduction to 90 degrees against resistance.

In a recent prospective study, Murrell and Watson [20] compared the results of 23 commonly used shoulder tests in 400 patients with and without rotator cuff tears. Three simple tests were found to be predictive for rotator cuff tears: supraspinatus weakness, weakness in external rotation, and impingement. In patients older that 60 years with 3 positive tests, there was a 98% chance of having a rotator cuff tear. If none were present, this was reduced to 5%. Furthermore, they conclude that the predictive power of the combined clinical tests is similar to the best values for magnetic resonance and ultrasonography.

Imaging of the Rotator Cuff

Advances in medical technology have included the development of increasingly sophisticated imaging techniques, which have greatly enhanced the surgeon's ability to diagnose, stage, and treat rotator cuff disease.

It is not surprising, however, that, considering the nature of rotator cuff pathology combined with the need to image both bone and soft tissue structures, no single imaging modality has been universally accepted as being the investigation of choice. As a result, a large amount of sometimes conflicting published literature compares various techniques with findings at arthroscopy and open surgery. Combining this with additional variables such as availability, cost, and interobserver variability means that further research in this field is needed before absolute consensus is achieved.

Those techniques most commonly used will be discussed:

Plain Radiographs

In early rotator cuff disease, plain radiographs are usually normal. With more advanced disease, and particularly in patients with positive impingement signs, radiographic abnormalities are found, but to visualize such abnormalities it is necessary to obtain specific radiographic views. Views commonly used to assess rotator cuff disease include the true anteroposterior (AP), scapular outlet views, and the 30-degree caudal tilt AP.

A true AP radiograph of the shoulder may show a reduced acromiohumeral interval of less than 7 mm, which suggests the presence of a chronic tear. Subacromial calcification or sclerosis (the "sourcil" sign), sclerotic changes in the greater tuberosity, or gross changes consistent with cuff tear arthropathy may be seen (Figure 12-6).

Acromial morphology is best visualized with a scapular outlet view, whereas the 30-degree caudal tilt AP view will demonstrate an anteroinferior acromial spur or calcification of the coracoacromial ligament.

Norwood et al. [21] give a comprehensive account of 10 radiographic abnormalities associated with rotator cuff disease, and attempt to correlate the number of abnormalities found with the severity of the underlying rotator cuff pathology.

Arthrography

Under normal circumstances, no communication exists between the glenohumeral joint and the subacromial bursa. Such a communication is prevented by the presence of the rotator cuff. This anatomical relationship forms the basis of shoulder arthrography. When radiopaque contrast is injected into the glenohumeral joint in the presence of a full-thickness rotator cuff tear, contrast will leak via the tear into the subacromial bursa, which can be visualized with plain radiography. For many years arthrography has been considered the gold standard technique to evaluate full-thickness rotator cuff tears. It has a false negative rate of 0% to 8% in published data (probably due to scarring and adhesions precluding contrast leakage), but it is accurate in only 50% of cases in predicting the size of such tears [22].

Positional arthrography is also accurate in demonstrating joint side partial-thickness tears seen as contrast extravasates along the cuff tendon. Attempts at improving resolution have been made using double contrast methods (dye and air), as well as computed tomography (CT). Unfortunately, there is no one method that will allow prediction of tissue mobility, ease of repair, and long-term function. However, CT arthrograms can be useful in attempting to address these issues. The combi-

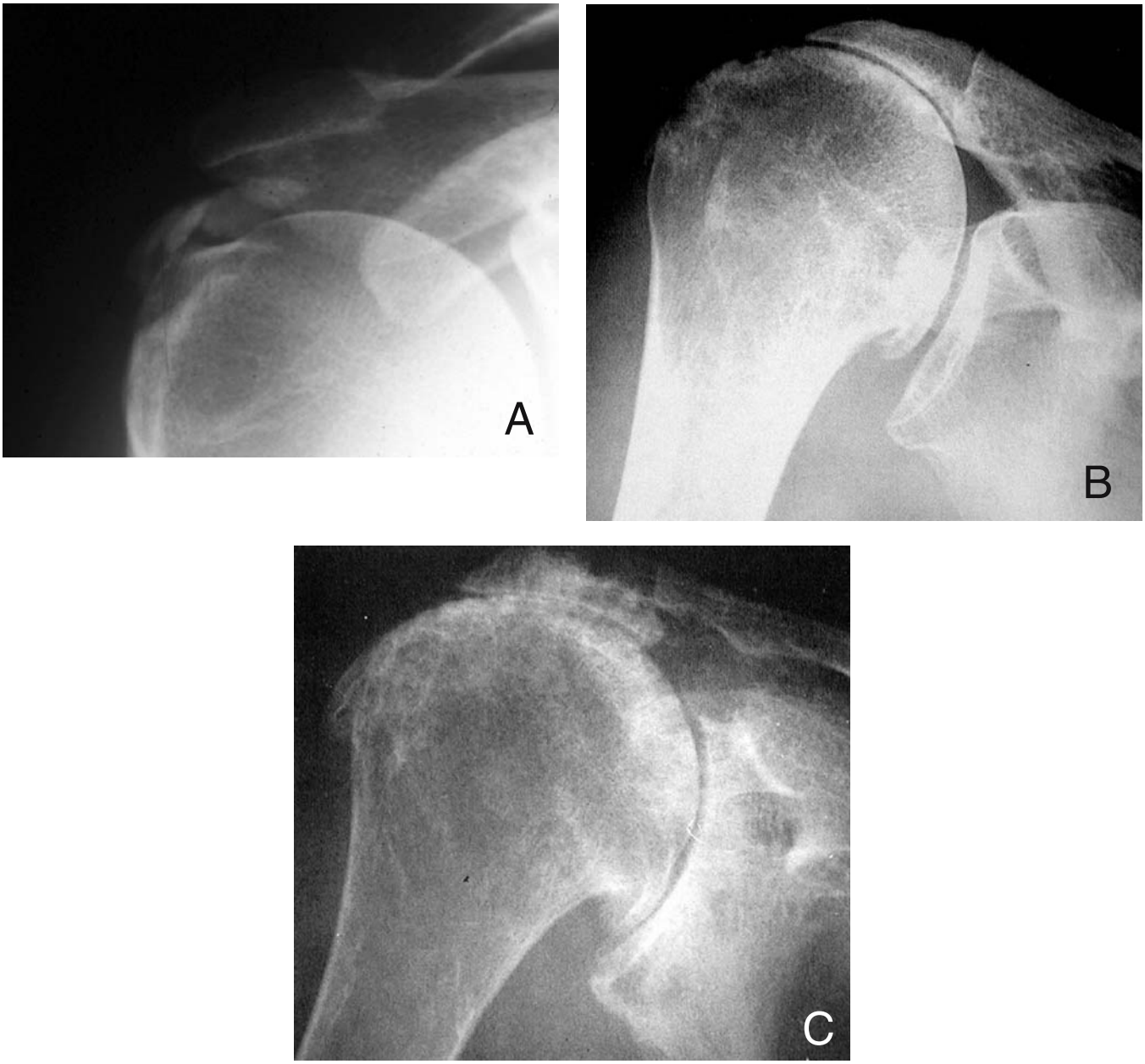

Figure 12-6. Plain radiographs showing features of rotator cuff disease. (A) Supraspinatus calcification. (B) Superior migration of humeral head. (C) Cuff tear arthropathy.

nation of arthrography and CT scanning enhances the quality of imaging of the glenoid labrum and glenohumeral capsule, as well as giving information about the degree of fatty degeneration within the torn rotator cuff. The degree of fatty degeneration of both supra- and infraspinatus is thought to be an important prognostic factor of the anatomical and functional results after rotator cuff repair. Goutallier et al. [23] proposed a 5-stage classification of such fatty degeneration based on CT scanning, and concluded that the degree of such degeneration had an influence on the final range of movement (particularly in external rotation) and the final strength. Furthermore, fatty degeneration after cuff tear has a strong association with the degree of tissue retraction [24] and muscle atrophy [25], both of which predispose to difficulties in achieving tear closure at operation.

Arthrography is unable to demonstrate bursal-sided partial-thickness tears. As in all partial-thickness tears, contrast cannot communicate with the subacromial bursa and, under these circumstances, no joint side discontinuity exists in the cuff to allow contrast to extravasate along the tendon. Subacromial bursography has been used to

detect bursal side partial tears, but the procedure is both impractical and inaccurate. Complications such as infection, allergic reaction, and synovial effusions are rare, but the procedure is invasive. As a result, there has been a general tendency away from arthrography.

Ultrasonography

Shoulder ultrasonography has been used to diagnose rotator cuff pathology since the early 1980s. It is an inexpensive, noninvasive modality that does not use ionizing radiation, and is widely available. Furthermore, it allows dynamic evaluation of the rotator cuff with results in real time and the important benefit of practical bilateral examinations. Its main drawback is that it is highly user dependent.

Ultrasonography can reliably detect full-thickness cuff tears (Figure 12-7). Teefey et al. [26] compared ultrasonography with arthroscopic findings in 100 shoulders. Ultrasonography correctly diagnosed all 65 full-thickness cuff tears (sensitivity 100%, specificity 85%) confirmed at arthroscopy and was accurate in predicting tear size in 86% of cases. Sensitivities of 96% and above for the detection of full-thickness tears are widely published.

Ultrasonography is much less reliable at detecting partial-thickness cuff tears. The distinction between a partial tear, tendinopathy, and cuff degradation can be very difficult. The presence of fluid in the glenohumeral joint and subacromial bursa correlates highly with the presence of a rotator cuff tear and is helpful in diagnosing partial tears. In the aforementioned study, 67% of partial-thickness tears were identified correctly by ultrasonography, but sensitivities of above 90% have been published.

Given its user-friendliness, cost, and performance in comparison with other imaging modalities, ultrasonography is now the "screening" modality of choice in the identification of rotator cuff tears.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) noninvasively produces high-resolution images of the bones and soft tissues of the shoulder, but, unlike arthrography, does not use ionizing radiation.

Its significant advantage is the diagnosis of midsubstance and bursal side rotator cuff tears, which allows detection of cuff pathology earlier in the disease process. Such tears can be difficult to diagnose with other imaging modalities. Bony pathology associated with rotator cuff disease may also be identified using MRI. Acromial morphology and subacromial spurs are easily demonstrated (Figure 12-8).

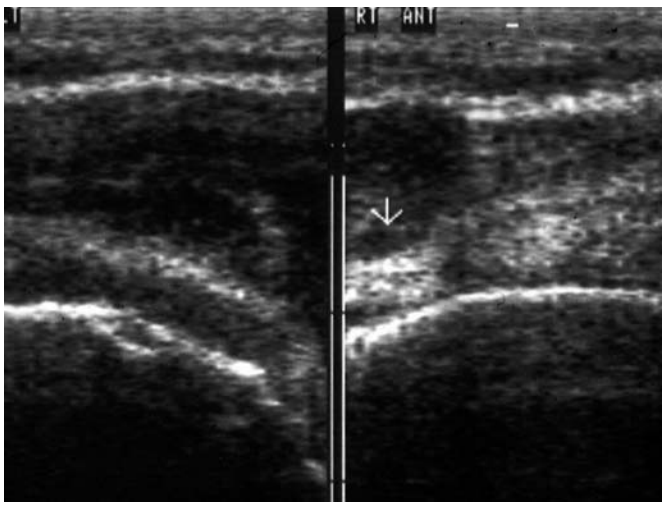

Figure 12-7. Ultrasound scan. (Left) Normal supraspinatus tendon. (Right) Full-thickness supraspinatus tear.

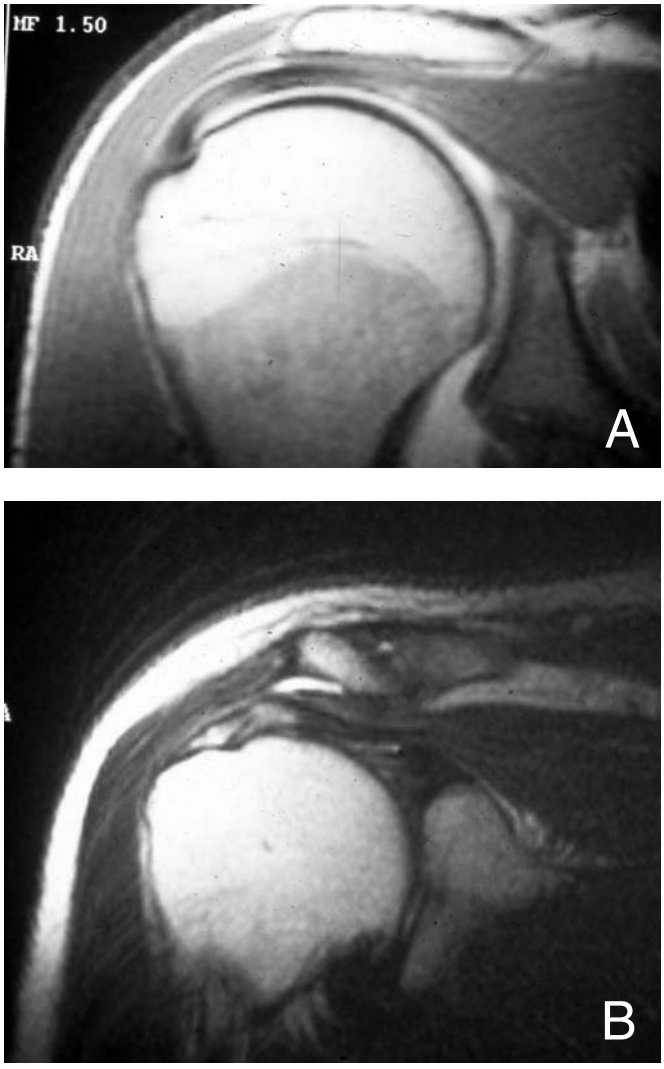

Figure 12-8. Magnetic Resonance Image. (A) Normal supraspinatus tendon. (B) Full-thickness supraspinatus tear.

As with ultrasonography, MRI is excellent at identifying full-thickness cuff tears. In Iannotti's series [27] comparing MRI with arthroscopic/open surgical findings, MRI had a sensitivity of 100% and specificity of 95% for full-thickness tears.

In addition, MRI offers information regarding cuff tear size, specific tendon involvement, and the degree of retraction. Tendon edges can be identified and comments made on the reparability of the tear. MRI can assist the surgeon in formulating a surgical strategy. However, MRI scans alone should not form the basis for surgery indications, as significant numbers of individuals with MRI-proven rotator cuff tears are in fact asymptomatic [8].

Arthroscopy

Diagnostic shoulder arthroscopy is indicated for the evaluation of the glenohumeral joint prior to arthroscopic subacromial decompression to rule out intra-articular or rotator cuff pathology. Concomitant pathological entities such as impingement, labral tears, and partial tears of the cuff on the articular side often exist.

Arthroscopy remains the definitive investigation in establishing the difficult diagnosis in the shoulder, all major pathological processes of the glenohumeral joint and subacromial space being amenable to arthroscopic diagnosis. It remains the benchmark by which other imaging modalities are compared (Figure 12-9, see color insert).

Despite this, arthroscopy should not replace, but instead enhance a detailed history, thorough clinical examination, and suitable radiographic tests, providing the indications and limitations of each are understood.

Management of Rotator Cuff Disease

Understanding what is the correct treatment for all forms of rotator cuff disease is both difficult and controversial. Patients with rotator cuff disease are a heterogeneous group, both in terms of their symptoms and underlying pathology. Furthermore, the methods and scoring systems used for functional assessment, symptoms, and quality of life evaluation as well as chosen outcome measures seem almost equally heterogeneous. Because of this, it is difficult to make comparisons and as a result draw sound conclusions from much of the vast array of published literature.

For the purpose of this chapter, an outline of the approach to the treatment of rotator cuff disease is offered, deliberately avoiding much of the minutiae and details of operative techniques that can be found in reference texts [28].

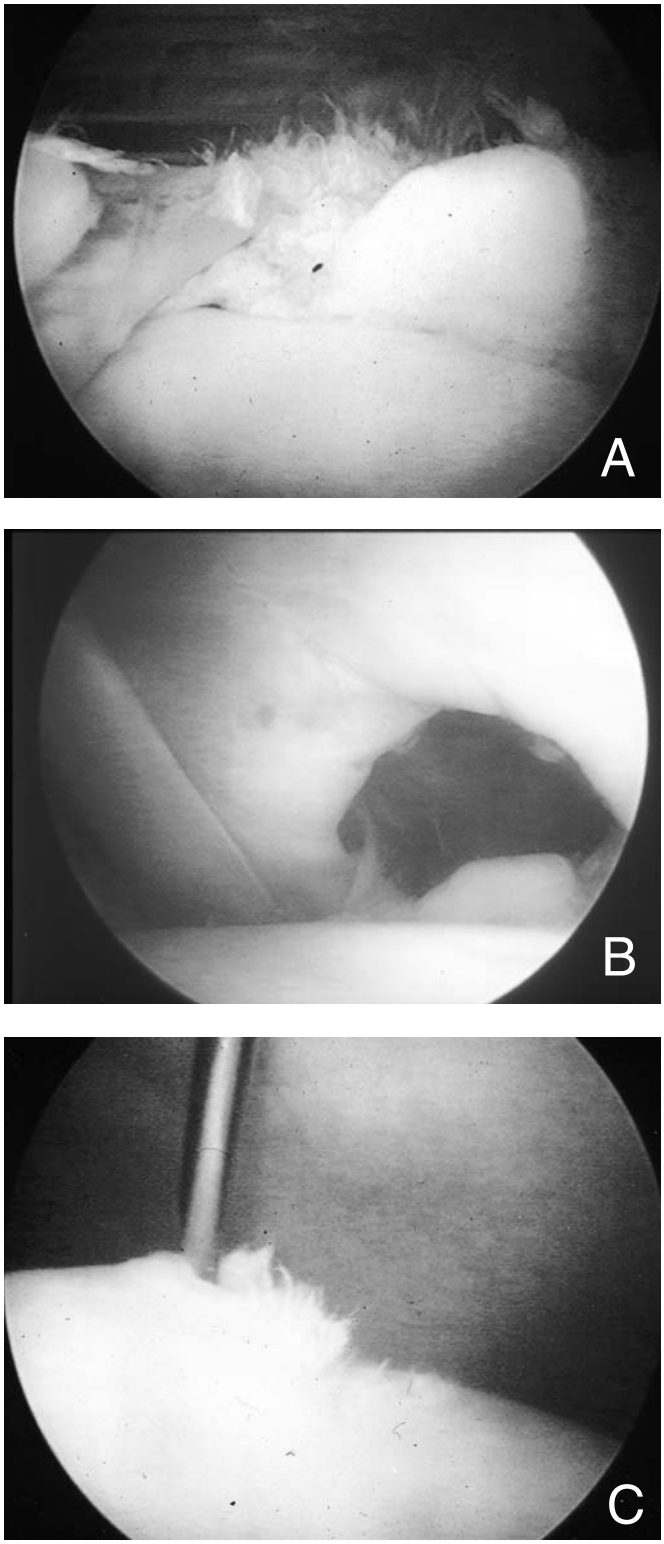

Figure 12-9. Arthroscopic appearances. (A) Bursal side full-thickness tear. (B) Joint side full-thickness tear. (C) Bursal side partial-thickness tear. (See color insert.)

Nonsurgical Management of Rotator Cuff Disease

The majority of shoulder surgeons will today recommend an initial trial of nonsurgical treatment for most patients with rotator cuff tears and would expect to continue this for at least 6 months before considering surgical intervention. Despite this, the length of nonsurgical treatment will vary depending on the degree of cuff involvement and with the patient's response to treatment. Continued pain despite an adequate rehabilitation protocol warrants consideration for surgical intervention.

The success of nonsurgical treatment has been reported from less than 50% to greater than 90%, and probably represents a lack of definitive indications for such treatment as well as variations in the protocols used. As a result, each patient needs to be individually assessed with regard to age, occupation, size of cuff tear, loss of function, mechanism of injury and, most importantly, pain.

Various nonoperative rotator cuff treatment programs have been described both for the general population and for athletes, and some surgeons devise individual treatment programs. Studies have consistently shown that better outcomes are achieved with well-structured, goal-directed rehabilitation programs tailored to each patient's specific needs. Within these programs a variety of treatment modalities can be used. These include:

1. Physiotherapy

Most physiotherapy regimes have common goals, which include the relief of pain, maintenance of good range of movement in the shoulder, and progressive strengthening of the rotator cuff, ultimately aiming for unrestricted movement. Typically patients are taught exercises which they need to perform several times per day for maximal benefit. Compliance is paramount, and regular patient review by the physiotherapist is important.

2. Nonsteroidal Anti-Inflammatory Medication

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used despite very little evidence as to their efficacy in the management of tendinopathies. Particular concern should be given to their side effect profile, specifically with respect to nephrotoxicity and gastrointestinal bleeding in older patients.

3. Corticosteroid Injection

Few studies conclusively show that subacromial injection of corticosteroids is of benefit in the treatment of rotator cuff disease. Blair et al. [29] showed a significant improvement in pain, range of motion, and relief of impingement signs in patients injected with 1% lidocaine and 80 mg triamcinolone compared with those receiving lidocaine alone. However, other studies have found no evidence of the efficacy of such treatments. Despite this, the design of studies investigating the efficacy of corticosteroid injections is highly variable. The systematic review of randomized clinical trials of corticosteroid injections by Van der Heijden et al. [30] highlights this. The poor methodology of the majority of studies is emphasized, while the more robust and better-designed trials provide little conclusive evidence as to corticosteroid injection efficacy. In parallel, but on a much broader scale, the systematic review of randomized control trials of interventions for shoulder pain by Green et al. [31] was equally critical. This included all randomized controlled trials of NSAIDs, subacromial corticosteroid injection, oral steroids, physiotherapy, manipulation under anesthetic, hydrodilatation, and surgery for shoulder pain. The only positive finding was that subacromial corticosteroid injection was better than placebo in improving the range of abduction, with little evidence to confirm or refute the efficacy of other interventions.

Adverse effects from subacromial corticosteroid injections are well known, with infection and tendon atrophy with rupture being reported. Tissue quality after repeated injection can be so poor as to render surgical repair impossible. In light of this, one can appreciate the potential hazard of making a diagnosis of "bursitis" or "tendinopathy" and treating the situation with repeated steroid injections until the realization of a major cuff tendon degeneration becomes apparent. Speed [32] gives an excellent review on the use of corticosteroid injection and recommends a maximum of 3 injections at one site with a minimum interval of 6 weeks between each.

4. Ultrasound and Phonophonesis

Ultrasound has been widely used for more than 30 years and, as with NSAIDs, little evidence exists to confirm its benefit in the treatment of rotator cuff disease. Ultrasound has a thermal effect on tissue causing local hyperemia, which is thought to be beneficial to the soft tissue healing process.

Phonophonesis is the use of ultrasound to enhance the delivery of topically applied drugs, e.g. nonsteroidals and steroid creams. Such topically applied drugs avoid the risk of systemic complications and eliminate first-pass hepatic metabolism. Published data offer good results, though most studies were poorly designed, incorporating many different musculoskeletal pathologies.

In the study by Morrison et al. [33] of 616 patients with positive impingement signs (mean follow-up 27 months), 67% had a satisfactory result with nonoperative treatment, while 28% with no improvement went on to have arthroscopic subacromial decompressions. Similarly, Itoi and Tabaton [34], in a 3- to 4-year follow-up of 114

patients with full-thickness cuff tears, report satisfactory results in 82% of patients treated conservatively.

Surgical Treatment of Rotator Cuff Disease

Shoulder surgery is technically demanding. Those surgeons with sufficient surgical expertise who can accurately select patients and perform the most appropriate operations for those patients consistently achieve the best outcomes. Patient selection can be difficult.

Patients with positive impingements signs, a failure of nonsurgical treatment, continued pain, and evidence of supraspinatus outlet narrowing are candidates for surgical intervention. Such patients may also have evidence of cuff degradation or partial-thickness tears. The indications for surgery on patients with full-thickness tears depend on the size of the defect and the mechanism of injury. Early surgical intervention is often warranted with acute tears, particularly in the younger patient who sustains a traumatic tear associated with marked functional impairment and weakness [35]. In chronic cuff tears with an insidious onset of symptoms, surgical treatment is only considered after a full nonsurgical rehabilitation program.

Full patient assessment is important. Other factors that may influence earlier surgical intervention include high premorbid activity, high expectations for future activity, and younger physiological age. Whenever a workers' compensation claim is an issue, both nonsurgical and surgical outcomes are less satisfactory. For this reason, compensation claims have been used as exclusion criteria in some studies.

Shoulder Impingement Syndrome

Approximately one-third of patients with shoulder impingement will continue to have pain and show positive impingement signs despite nonoperative treatment. The majority of these patients will undergo acromioplasty.

Open decompression of the subacromial space was first described by Neer [16] in 1972. Ellman [36] published the first large series of 50 arthroscopic decompressions in 1987.

Arthroscopy is now generally favored. Proponents have argued that this procedure requires less surgical dissection and produces less scarring or postoperative morbidity. Additionally, cosmesis is good, and patient acceptance is high. Arthroscopy offers the ability to inspect the glenohumeral joint and subacromial space, as well as identifying any partial or full-thickness rotator cuff tear that may coexist.

Despite this, the goals for both open and arthroscopic techniques are identical. Subacromial decompression should recontour the acromion such that its undersurface is smooth and flat, impingement relieved, and pain alleviated. Recovery takes 2 to 4 months, with 83% to 94% of results proving satisfactory. As this procedure is carried out to relieve pain, such results are entirely dependent on the patient's subjective interpretation of their pain levels at review.

Less commonly, acromioclavicular resection is employed. Acromioclavicular arthritis or joint osteophytes can result in impingement and mechanical irritation of the cuff tendons. In this technique, 1.0 to 1.5 cm of the distal clavicle are excised, using either open or arthroscopic techniques, leaving a flat and smooth bone surface while preserving the superior and posterior capsular ligaments for stability.

Partial-Thickness Tears

Partial-thickness tears of the rotator cuff are common, with the majority of such tears occurring on the articular surface of the supraspinatus insertion site. Partial tears are not a single condition, but represent the common outcome of a variety of insults to the rotator cuff. Degenerative changes due to aging, anatomical impingement, and trauma may all be etiological factors. Because of this, several approaches to surgical treatment exist in the event of failed nonsurgical treatment.

There is no surgical treatment that reliably restores the tendon to its normal condition. Historically, arthroscopic debridement of the cuff defect and subacromial decompression have been used, either singularly or combined, with good results. Open repair by excision of the partial tear defect and repair of the subsequent full-thickness tear has also been used. The use of either technique is determined by the size of the defect, acromial morphology, age, and activity level of the patient.

For patients with significant supraspinatus outlet narrowing and partial-thickness tear of the supraspinatus alone with a defect involving <50% of cuff thickness, subacromial decompression alone, with or without arthroscopic debridement of the cuff tear, provides good or excellent results in the majority of cases. In younger patients or those with high functional demands and a tear of >50% of cuff thickness, open repair may be necessary, with or without subacromial decompression, depending on acromial morphology. In the series of 39 patients [37] with partial-thickness tears treated with debridement, decompression, and tendon repair, 90% regarded their general condition as improved at review (mean 55 months).

Full-Thickness Tears

Many patients with full-thickness cuff tears have excellent outcomes with nonsurgical treatment. In those who do not improve, open surgical repair is commonly undertaken. While the diagnosis of a full-thickness tear is not difficult, it is important to realize that in a small group

the cuff defect is irreparable due to the poor quality of the underlying tissues.

The greatest challenge in this type of surgery is dealing effectively with the torn retracted cuff tendons. The fresher the tear, the easier it is to repair and the less traction is required to bring the tendons back to their near normal anatomical position—re-rupture being one of the major complications of such surgery. Chronic tears are characterized by significant retraction and fibrosis, often necessitating partial resection of the thickened and proliferative subacromial bursa to delineate cuff tendon anatomy.

Usually irreparability can only be determined on inspection of the tissues, but information bearing on the reparability of the cuff defect can sometimes be obtained from the history and examination. Acute tears in younger, healthy patients are more likely to be reparable. Long-standing tears associated with major weakness in older patients carry a poorer prognosis. The prognosis for a durable repair is even worse if the history reveals local or systemic steroid usage, smoking, or previous surgery.

Several series have reported the results of surgery for full-thickness rotator cuff tears. Most describe clinical results that, on average, support satisfactory (good or excellent) result in 85% to 90% of patients [38]. Preoperative cuff tear size strongly correlates with other prognostic factors, including tendon tissue quality and the difficulty of tendon mobilization. Women with associated rupture of the long head of biceps often did worse.

It is not within the scope of this chapter to describe detailed surgical procedures; the reader is referred to reference textbooks.

Massive Tears

With massive tears, the complexity if the problem is magnified. Cofield suggested that tears greater than 5 cm should be termed massive, whereas Patte requires a tear diameter of 5 cm with acromial migration and glenohumeral arthrosis to consider a tear massive. Lack of uniformity in classification schemes makes it difficult to perform comparative research, and it is a source of controversy in diagnosis and management of such injuries. Disagreement also exists as to whether surgical results on patients with massive tears are affected by tear size. It appears that surgery for patients with massive tears is better at eliminating pain than improving function.

A multitude of surgical techniques exist for the surgical management of massive cuff tears. In patients with an irreparable cuff tear, debridement and decompression is thought to be the treatment of choice by many surgeons. Those patients whose main complaint is pain with an intact anterior deltoid and long head of biceps do best. Both short- and medium-term results have been satisfactory, however these initial results have been seen in some studies to deteriorate with time. Any decompression should leave the coracoacromial arch intact. This structure is thought to prevent superior migration of the humeral head, especially in the presence of massive cuff tears, which may otherwise predispose to cuff tear arthropathy.

Many techniques for local rotator cuff repairs or muscle transfers have been described, for example using subscapularis or teres minor. Depending on the size of the tear and mobility of the muscle, these techniques may or may not be suitable to close massive rotator cuff defects. If unsuccessful, many other techniques have been described, and include distant muscle transfers, for example using trapezius or latissimus dorsi, and autogenous free fascia lata grafts.

Despite this, reconstruction of the rotator cuff may not eliminate end-stage rotator cuff arthropathy and pain. Treatment in these circumstances, as with the majority of rotator cuff surgery, is aimed mainly at the resolution of the patient's pain. Function is almost always improved with relief of pain, but functional goals are variable. Possible methods of treatment include conservative treatment, glenohumeral arthrodesis, resection arthroplasty, hemiarthroplasty, and total shoulder arthroplasty. Almost all published series of surgical management show very high complication rates.

Complications of Rotator Cuff Surgery

Patient selection is crucial for satisfactory outcomes in rotator cuff surgery, and good results can be expected if careful selection criteria are employed by a suitably skilled surgeon. With poor patient selection, complication rates increase. Such complications may be related to misdiagnosis, errors of technique, or unforeseeable postoperative factors such as poor rehabilitation and wound healing problems.

Complications Relating to Misdiagnosis

With a detailed history and examination, the diagnosis of impingement or a symptomatic rotator cuff tear can usually be made with a high degree of confidence. Conversely, the role of taking a history and performing a detailed clinical examination is to enable the surgeon to confirm or exclude other differential diagnoses that may be responsible for a patient's symptoms.

Other diagnoses that must be excluded include those related to referred pain such as cervical radiculitis, thoracic outlet syndrome, and suprascapular nerve entrapment. Intra-articular pathology, such as glenohumeral instability, arthritis, labral tears, or adhesive capsulitis may be present, as may extra-articular conditions including acromioclavicular joint arthritis and unrecognized rotator cuff tears. Occasionally, issues relating to sec-

ondary gain may be pertinent either in the form of compensation claims or in patients with psychiatric disorders. Furthermore, impingement and rotator cuff tears may occur with a secondary, coexistent pathology, which may complicate the diagnostic process.

Complications Related to Decompression

The deltoid, in concert with the rotator cuff, is responsible for generating synchronized and powerful glenohumeral motion. Deltoid detachment is a serious complication that results in significant disability, often in excess of the presence of an isolated cuff tear. Detachment typically occurs in the first 6 weeks postoperatively and is diagnosed clinically by observing a defect at the deltoid origin and a bulge in the deltoid muscle distal to its normal origin. Magnetic resonance imaging may confirm the diagnosis. Risk factors for deltoid detachment are complete or lateral acromionectomy, infection/hematoma, trauma, and early aggressive resistive physiotherapy. This complication has recently been reported with arthroscopic techniques.

Both conservative and surgical treatment (with reattachment or rotational deltoplasty) have shown poor functional results, and prevention of this disabling complication is stressed.

Neer has been credited with describing the anatomical importance of the anterior edge and undersurface of the anterior third of the acromion, coracoacromial ligament, and, in some cases, acromioclavicular joint in impingement. Inadequate decompression is one of the most common causes of poor results after performing acromioplasty. In cases where partial lateral acromionectomy has been performed, a significant number of patients continue to have symptoms because a portion of the "impingement anatomy" persists. Also, inadequate decompression has been associated with poor judgment regarding the amount of bone to be resected with respect to the anterior acromioplasty.

Acromial fracture is an infrequent complication of both open and arthroscopic acromioplasty, and has been associated with deltoid avulsion. Fracture is associated with overaggressive decompression (especially in osteoporotic bone) and, although rare, problems with healing are common (even with surgical intervention), resulting in pain and severe limitation of movement. Prevention by attention to careful surgical technique is therefore important to prevent this infrequent but significant complication.

Occasionally, symptoms of impingement recur as a result of heterotopic ossification at the site of previous acromionectomy. Rates of 3.2% are being reported. Risk factors include hypertrophic pulmonary osteoarthropathy, active spondylitic arthropathy, and chronic pulmonary disease.

Complications Related to Rotator Cuff Repair

Numerous techniques have been described for rotator cuff repair, particularly for large and massive tears, but no technique had been immune from the problem of recurrent tears. Recurrent tears have been attributed to size of tear at time of repair, inadequate tendon mobilization at operation, poor fixation techniques, trauma, and spontaneous rupture. Decompression of the subacromial space has been recommended as a concomitant procedure with rotator cuff repair. In addition to pain relief, the risk of recurrent tear is also reduced.

Neurological injury is a rare complication of rotator cuff surgery. Most commonly the axillary nerve is involved, but subscapular nerve injury is also reported. Most cases of axillary nerve injury are a result of overzealous deltoid retraction during deltoid splitting approaches, and are most frequently associated with an aberrant nerve course. Diagnosis is with electromyography.

Complications Related to Rehabilitation

Prolonged postoperative immobility, poor compliance, and deltoid detachment may result in a frozen shoulder. Treatment may be nonoperative with further physiotherapy, although manipulation under anesthetic or adhesion release may be needed. Less frequently encountered complications include reflex sympathetic dystrophy and rupture of long head of biceps.

Complications Relating to Wound Healing

Deep infections are rare, but necessitate aggressive management with drainage, debridement, and lavage, as well as culture-specific antibiotics. Such infections result in a significant negative impact on the final outcome of surgery. Less frequent complications include draining sinuses, suture granulomas, and keloid scars.

Treatment Failure

1. Failed Acromioplasty

In these circumstances, patients are dissatisfied with the results from previous arthroscopic or open acromioplasty, and usually continue to have marked pain. Such results occur in all series of acromioplasty, with incidences of failure ranging from 3% to 11%.

Treatment failure may be due to the presence of coexisting pathology. Diagnoses other than continuing impingement, including acromioclavicular joint problems, cervical spondylosis, thoracic outlet syndrome, and rotator cuff tears have been found in up to 45% of cases of failed acromioplasty. As previously mentioned, patients with workers' compensation claims often have poor outcomes even after revision surgery.

Other causes of failed acromioplasty include failure to achieve subacromial smoothness, failure of deltoid reattachment, excessive acromial resection, and postoperative complications such as dense scarring and poor rehabilitation.

Patients with unsatisfactory primary surgery need careful evaluation from a clinical, social, and vocational perspective. Often a nonsurgical treatment protocol may be commenced (even if this has previously been unsuccessful), and further imaging may be necessary.

Reoperation is considered in those well-motivated patients with residual subacromial "roughness." Patients with refractory shoulder stiffness may also be offered reoperation, as scarring between the acromion and rotator cuff cannot be managed nonoperatively. The revision procedure is usually identical to the primary acromioplasty.

Failed Rotator Cuff Surgery

Poor outcomes for rotator cuff surgery may occur for many reasons. Failure to ascertain patient expectations, infection, deltoid denervation or detachment, failure of cuff repair, and failure of rehabilitation are but a few causes.

Effective management of treatment failure depends on establishing the correct diagnosis. Infection needs culture-specific antibiotics, irrigation, and drainage if pus is present. Failure of deltoid reattachment needs prompt surgery before retraction becomes fixed. Chronically painful and functionally limiting scarring often responds to stretching exercises. Shoulder manipulation is not advisable due to the risk of cuff damage, but open lysis and removal of adhesions may be beneficial.

Persistent weakness needs evaluation for neurological injury or cuff failure, with denervation injuries being diagnosed with selective electromyography. Cuff failure is suggested by weakness of external rotation or abduction and superior instability of the humeral head. Dynamic ultrasonography is useful in such situations. Repeat cuff explorations with debridement or repair may be considered, but the risks of finding poor-quality tissues should be explained to the patient. Superior instability can result from loss of the coracoacromial arch without reestablishing stability with a durable cuff repair causing significant morbidity.

Results for revision cuff surgery are inferior to those for primary repair. DeOrio and Cofield found that at an average of 4 years after repair, 76% of patients had sustained diminution of pain but 63% still had moderate or severe pain [39].

In cases where a shoulder had been devastated by infection, denervation, or intractable cuff failure, consideration is given to arthrodesis. The best candidates for this procedure are those patients with severe weakness, good bone quality, and a good understanding of the limitations and complications of the procedure.

Conclusion

Many aspects of rotator cuff disease are controversial, and further research is necessary in areas such as imaging, pathophysiology, and natural history to further our understanding of the disease and make improvements in diagnosis and treatment.

Many questions remain to be answered. What causes pain in rotator cuff disease? Why are some patients asymptomatic? What role does genetics have in rotator cuff disease, and could prevention be possible? More theoretical concepts such as preoperative assessment systems and outcome measures need to be standardized to facilitate comparative research and provide statistical power to evidence-based management. A uniform method of classification for rotator cuff tears would also be welcomed.

Patients with rotator cuff disease are a heterogeneous group, and because of this an individualized approach based on a detailed history and clinical examinations is vital. Despite this, rotator cuff disease represents a complex clinical challenge, and therefore its management should very much remain in the hands of the specialist shoulder surgeon.

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13
Rotator Cuff Disorders

Theodore A. Blaine and Louis U. Bigliani

Introduction

Disorders of the rotator cuff tendons were first recognized early in the 19th century. An account of J.G. Smith (1835) described a tear that occurred as a result of a "severe blow, strain, or dislocation" of the shoulder [1]. The first surgical procedure to repair the injured rotator cuff tendon was described by Codman in 1911 [2]. Techniques were further modified by McLaughlin, and later by Neer [3–7]. Recent advances have emphasized minimally invasive techniques for subacromial decompression and rotator cuff repair, including arthroscopic and "mini-open" approaches.

Despite the advances in both diagnosis and surgical management of rotator cuff disorders, the exact etiology of rotator cuff tendinopathy is not fully understood. Both intrinsic and extrinsic theories of tendon injury have been proposed. Meyer suggested an extratendinous theory in 1922 where "tendon and capsular tears" were thought to be "secondary to frictional contact of the greater tuberosity on the acromion [8]." This theory was contrary to that proposed by Lindblom in 1939, where injury was thought to be secondary to "tension in the fascicles of the tendon aponeurosis [9]." Codman later emphasized the contribution of trauma to tendon injury. Finally, Neer turned the focus of etiology back to the acromion when he described "impingement syndrome" in 1972 [6]. More recent research has implicated the subacromial bursa as part of the pathology, with increased inflammatory mediators, afferent nerve endings and their products in inflamed subacromial bursa [10–14]. Currently, rotator cuff tendinopathy is considered to be multifactorial in etiology, and the relative contributions of these factors remain to be determined.

Rotator cuff tears are common, and their incidence increases with advancing age. Major and minor trauma can be associated in up to 58% of patients, and the incidence is particularly high in overhead athletes (30%) and laborers (23%) [15]. Nonoperative management is successful in the majority of patients, although these results are highly variable and depend upon several patient factors including patient age, tear size, and functional level [16–18]. Surgical principles of rotator cuff repair are much the same as those proposed by McLaughlin in 1944: reestablish the continuity of the cuff mechanism, obtain a tension-free repair, and create a smooth acromial surface to limit extrinsic impingement [4]. With current operative techniques, recent series have reported good to excellent results in both functional improvement (70% to 95%) and pain relief (85% to 100%) [19–28].

Patient Evaluation

Pain is the most common complaint in patients with rotator cuff disease. While sudden trauma can cause acute rotator cuff tears, especially in association with shoulder dislocation, the pain of rotator cuff disease often occurs insidiously, and usually cannot be related to a specific inciting event. The pain may often radiate down the arm, but does not localize below the elbow. This radiation of pain is attributed to the subacromial and subdeltoid bursa, which is rich in nerve endings and extends down to the deltoid insertion on the arm. Pain is usually aggravated by overhead activities, but rest pain and night pain may also be present. In addition to pain, the patient may also complain of weakness and inability to raise the arm. These complaints are often indicative of a larger size tear.

Physical examination should include visual inspection to determine the presence of deltoid or spinati muscle atrophy. Rupture of the biceps tendon may be manifest by a bulge in the proximal arm, while the presence of a "fluid sign" may indicate a massive rotator cuff tear consistent with rotator cuff tear arthropathy. Ecchymosis may be present in the setting of acute injury. Palpation should be performed to determine the presence of tenderness over the greater tuberosity and also to assess associated acromioclavicular joint tenderness.

Both passive and active range of motion should be examined. While passive range of motion is usually preserved with rotator cuff tears, mild stiffness from posterior capsular tightness can exacerbate impingement symptoms, while a secondary adhesive capsulitis may also rarely occur. In patients with severe impingement, an "arc of pain" will be present with passive motion. Provocative tests should be performed, including both the Neer and Hawkins impingement signs. The Neer impingement sign is elicited with passive forward elevation of the arm in the scapular plane. A positive Hawkins impingement sign is present when internal rotation of the arm when abducted to 90 degrees produces pain in the subacromial space.

While strength may be normal in some patients with small full-thickness rotator cuff tears, weakness is usually present with larger tears. Occasionally, pain will complicate the clinical exam and a subacromial lidocaine injection may be useful to distinguish pain from true weakness. Strength in forward elevation and external rotation should be closely examined. Patients with large tears have a positive "lag" or "drop" sign, indicating weakness of external rotation. A positive drop sign—inability to maintain neutral rotation with the arm at the side—usually indicates a tear of the infraspinatus and teres minor. Often patients with massive tears cannot actively elevate the arm above 90 degrees. Patients with nonpainful weakness require an expanded differential diagnosis. Neurologic lesions, including cervical radiculopathy, brachial neuritis, suprascapular neuropathy, or syringomyelia must be considered. Specific attention should be paid to potential tears of the subscapularis tendon, which often are undiagnosed. These are more common in the setting of acute trauma and anterior shoulder dislocation, although they may also occur in chronic massive rotator cuff tears. The "lift-off" and "belly-press" tests are useful in diagnosing subscapularis tears [29].

Radiographic Evaluation

Routine radiographic evaluation should include supraspinatus outlet, axillary, and anteroposterior (AP) radiographs in neutral, and in internal and external rotation. The supraspinatus outlet view is performed with a 10 degrees caudal tilt to the X-ray beam, and is particularly useful for assessing acromial morphology and the presence of an acromial spur (Figure 13-1). Three distinct acromial shapes have been described by Bigliani [30]. Type I, or "flat" acromions and type II "curved" were rarely associated with rotator cuff tears, while type III "hooked" acromions are associated with rotator cuff tears in 70% of postmortem specimens. The outlet view should also be examined for the presence of acromial "spurs," which indicate coracoacromial ligament degenerative changes and osteophyte formation, which are distinct from the acromial shape.

The axillary view is important to rule out the presence of os acromiale, which is present in 1% to 3% of the population, and is bilateral in 60% of patients. The AP view is particularly helpful in estimating the acromiohumeral interval, typically 1 to 1.5 cm [31]. Patients with large or massive tears have a decreased acromiohumeral distance. In our series of massive tears, the average acromiohumeral interval was 7.1 mm. Early signs of cuff tear arthropathy must be considered in patients with superior migration of the humeral head, superior glenoid wear, and erosion into the acromioclavicular joint [32]. AP views in internal and external rotation can also be helpful in identifying calcific tendonitis, which can be missed on a single AP view.

Further imaging may be necessary in the patient who has not responded to non-operative management.

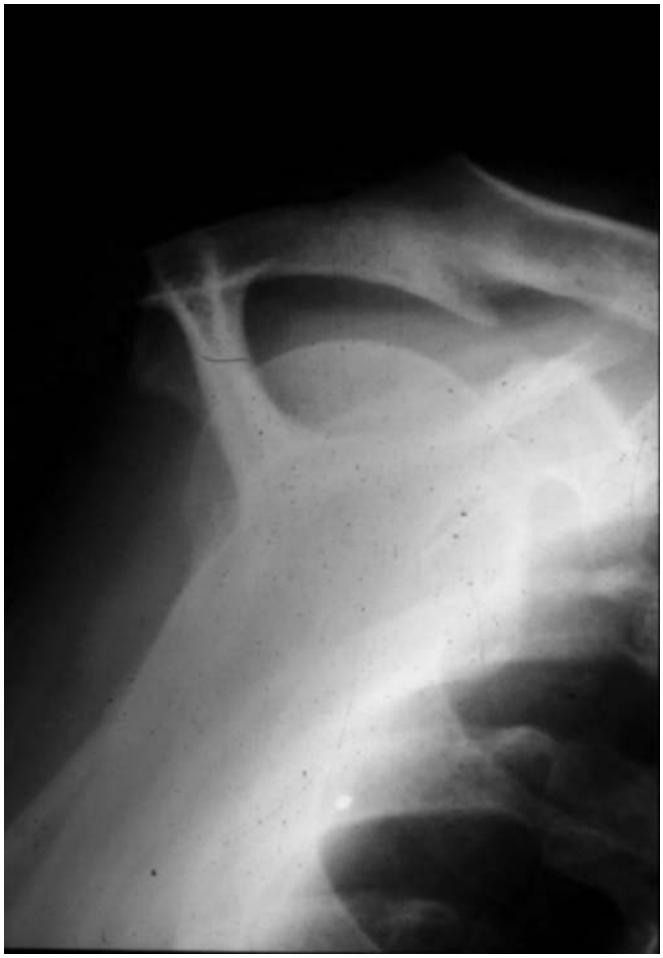

FIGURE 13-1. The "outlet view" is taken with the X-ray beam tilted 10 degrees caudally. This view is important in determining acromial morphology and the presence of "spur" formation in the coracoacromial ligament.

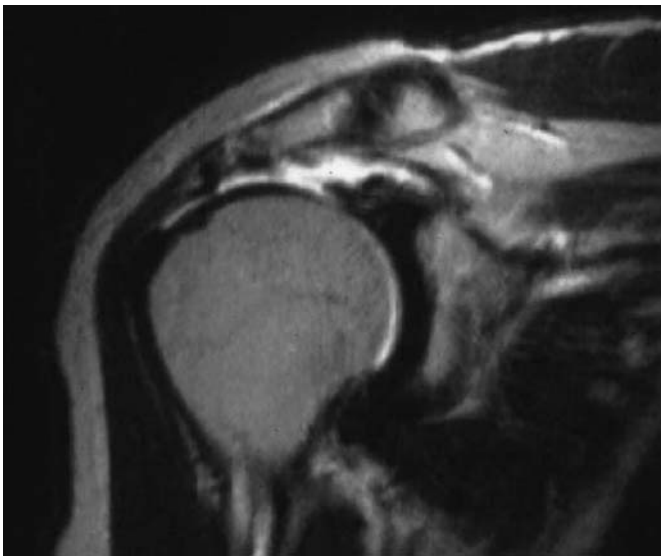

FIGURE 13-2. The MRI scan is the most useful test for evaluating rotator cuff tears. A large tear of the supraspinatus is evident on this oblique coronal image.

Arthrography, ultrasonography, and magnetic resonance imaging (MRI) can confirm the presence or absence of a rotator cuff tear. MR imaging is the preferred modality, as information regarding tear size, tear location, and tissue quality can be more clearly elucidated [33] (see Figure 13-2). It is important to obtain MR images in the scapular plane to evaluate the infraspinatus attachment and more proximal cuts to determine muscle atrophy [34]. Atrophy of the spinati muscles may predict the inability to obtain complete repair of the rotator cuff. Axillary images are needed to evaluate the subscapularis tendon and subluxation, dislocation, or rupture of the long head of the biceps. MR imaging is also useful in assessing the quality and size of the coracoacromial ligament, as thickening of the anteromedial band can be associated with impingement syndrome and rotator cuff tears in some patients [35].

Classification

The size of the rotator cuff tear is usually determined at the time of surgery, but can also be estimated on the MRI scan. The size of the tear is measured by the width of the tear at its insertion to the greater tuberosity or by its greatest diameter in any direction. Small tears are less than 1 cm wide; medium tear are 1 to 3 cm; large tears 3 to 5 cm, and massive tears greater than 5 cm wide [36]. The number of tendons involved can also characterize the tear, although this system may be unreliable due to confluence of the tendons at their insertion into the greater tuberosity [37]. Large and massive tears typically involve two or more tendons.

Management

Nonoperative

Nonoperative management of rotator cuff tears and impingement syndrome can be successful in 33% to 92% of patients. Management consists of rest and avoidance of provocative activities. A trial of nonsteroidal anti-inflammatory medication should be attempted if not contraindicated. Physical therapy can be very helpful in maintaining motion, increasing rotator cuff strength, and decreasing inflammation and pain. Passive range of motion exercises should be combined with resistive exercises with the arm below the horizontal. Therapeutic modalities, such as heat, ultrasound, ionophoresis, and phonophoresis can also be of value.

When these nonoperative management modalities are unsuccessful, consideration should be given to subacromial injection of steroid medication. Usually no more than three injections should be performed before the patient is counseled to have surgical management. Injections have also been found to be less helpful in the presence of large or massive rotator cuff tears.

Surgical Management

Indications

Because rotator cuff tears can be present in the general population in the absence of symptoms or functional deficits, the presence of a documented rotator cuff tear alone does not require surgery. However, when a rotator cuff tear is identified in combination with pain or functional deficit that is not responsive to conservative management, surgery is indicated. Nonoperative management is typically continued for 3 to 6 months before surgery is contemplated. More urgent surgery may be necessary in young patients with acute tears and in older patients who have acute extensions of chronic tears. The ability to repair the cuff may be improved in these patients when surgery is performed within the first 3 weeks after injury [38].

Arthroscopic Management

Arthroscopic acromioplasty and rotator cuff repair is advantageous due to the improved cosmesis and preservation of the deltoid origin. It is also useful in identifying the presence of associated pathology which can occur in up to 60% of patients [39]. Arthroscopy is performed with the patient in the beach-chair position so that conversion to an open procedure is possible. The glenohumeral joint is entered from a posterior portal and the rotator cuff insertion is inspected. Partial-thickness tears may be identified on either the articular or bursal side of the tendon. If the partial thickness tear is found to be less

than 50% of the tendon width, no repair is needed and a subacromial decompression alone will suffice. However, if the tear is greater than 50%, debridement of the tear and primary repair either through arthroscopic or mini-open techniques is recommended.

Impingement may occur from the anteroinferior acromion, a hypertrophied coracoacromial ligament, or hypertrophic changes at the acromioclavicular joint. Bursectomy is performed through one or two lateral portals, and the coracoacromial ligament is detached from its insertion along the undersurface of the acromion. Arthroscopic acromioplasty creates a smooth undersurface to the acromion, with care to avoid detachment of the deltoid origin. Once acromioplasty is complete, the bursal side of the rotator cuff is inspected for full thickness tears (see Figure 13-3). When a tear is identified, the remaining rotator cuff must be mobilized by releasing intra-articular and subacromial adhesions.

Multiple techniques have been described for suturing the tendon and securing it to the tuberosity [40,41]. We prefer to use the absorbable suture anchors because of their ease of insertion. A spinal needle is used to determine the appropriate location at the tuberosity for anchor insertion, and a drill hole for the suture anchor is made through a small stab wound at this location. The Caspari suture punch is then used to create a passing suture (double limbed #2–0 Prolene or a shuttle relay device) (see Figure 13-4). The suture anchor is placed in the hole and one limb of the suture is passed through the tendon and back out the lateral hole with the passing suture (see Figure 13-5). Both limbs of the anchors are then withdrawn from the lateral portal and the sutures may then be tied down using the surgeon's arthroscopic knot of choice.

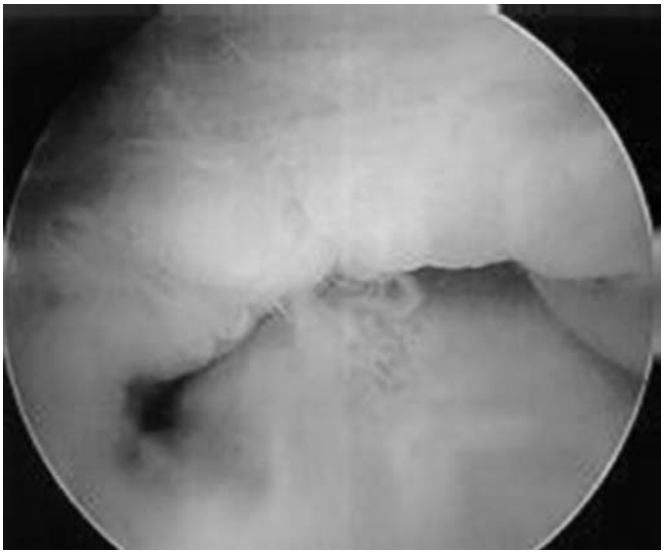

FIGURE 13-3. A full thickness tear of the supraspinatus tendon is seen with the 30-degree arthroscope in the subacromial space.

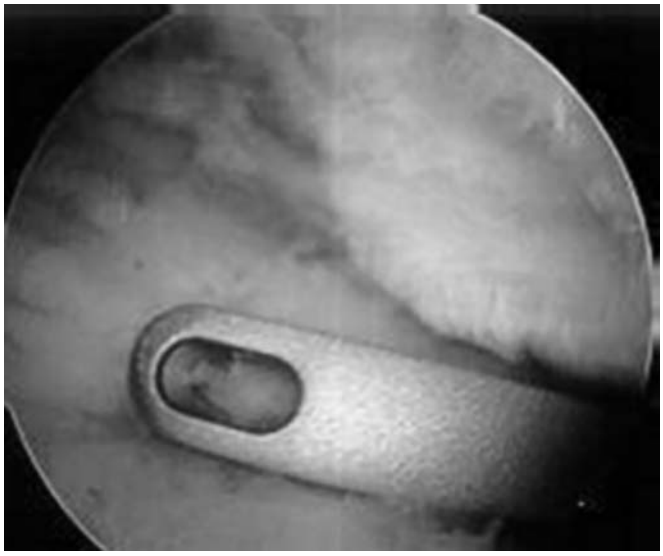

FIGURE 13-4. The tendon edge is grasped with the Caspari suture punch, and a passing suture is advanced through the tendon.

The results of arthroscopic management of rotator cuff tears are still being determined. Various techniques have been advocated for successful repair, with early good to excellent results reported in 84% to 92% of patients [42,43]. However, the technique is technically demanding and these results may not be reproducible for all orthopedic surgeons.

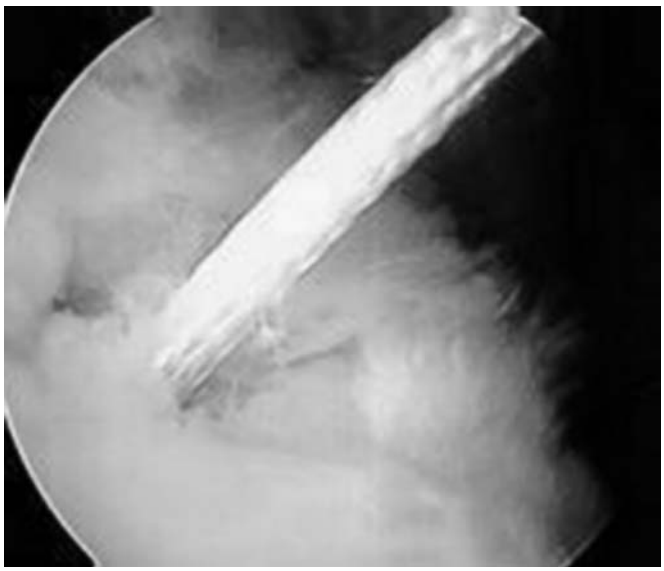

FIGURE 13-5. An absorbable suture anchor is placed in the anchor hole, and one suture limb is passed through the tendon edge with the passing suture.

Mini-Open

Mini-open rotator cuff repair has combined the advantages achieved by arthroscopic acromioplasty with the advantages of open rotator cuff repair. The incision is smaller than the standard open cuff incision, and the deltoid origin is preserved. Cuff mobilization can also be performed arthroscopically before the mini-open incision is made. Unlike the arthroscopic repair, direct visualization can then be achieved, thus assuring that complete mobilization of the rotator cuff to the tuberosity is performed.

Small or medium-sized rotator cuff tears are approached through a mini-open portal extending incision of approximately 3 cm following an arthroscopic anterior acromioplasty. The deltoid is then split in line with its fibers to the lateral edge of the acromion and 3 to 5 cm laterally. Richardson retractors and manipulation of the arm allows the entire cuff tear to be seen (see Figure 13-6). Repair of the tendon to the tuberosity can then be a done with either suture anchors or with transosseous bone tunnels and non-absorbable suture. Despite the excellent application of this technique to small and medium sized tears of the supraspinatus and infraspinatus tendons, access to the subscapularis and teres minor is difficult and open repair is recommended for larger-sized tears.

Open Repair

The repair of large and massive tears remains a technical challenge. Significant tendon retraction, bursal scarring, and adhesions to adjacent structures often accompany massive tears [44,45]. While local tendon transposition, tendon transfers, and tissue grafting with autograft, allograft, and synthetic material have all been described as potential options in repairing or augmenting the cuff repair, greater satisfactory results have been attained in studies using mobilization or transposition of existing rotator cuff tissue [46–52]. An anterosuperior approach to the shoulder is used with a deltoid split of less than 3 to 4 cm. The coracoacromial ligament is released but preserved in order to prevent postoperative anterosuperior humeral head subluxation [53,54]. While lateral or radical acromioplasty should be avoided to prevent deltoid dysfunction, an anterior acromioplasty should be performed as part of the procedure [55–60]. A complete acromioclavicular arthroplasty or distal clavicle resection is reserved for patients who are symptomatic on clinical exam with associated tenderness and pain with cross-body adduction. The resection should allow for preservation of the superior acromioclavicular ligaments to maintain anterior-posterior stability of the joint.

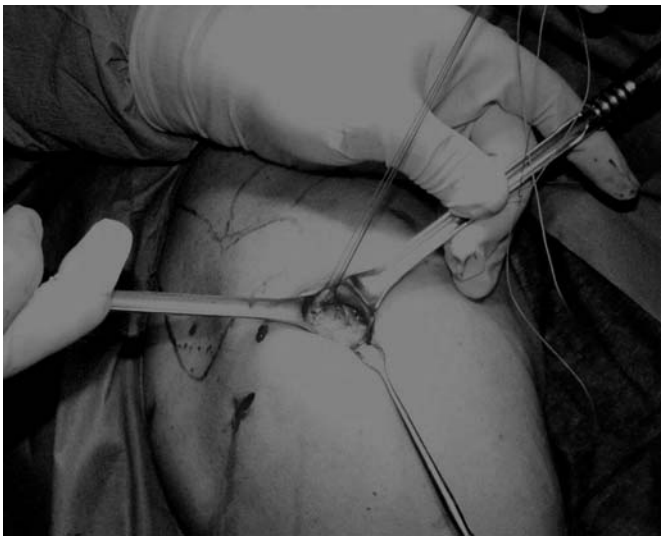

FIGURE 13-6. A deltoid split is made for the mini-open approach. Retractors are placed, and the arm is manipulated to expose the rotator cuff tear. A tear of the supraspinatus tendon is identified.

The rotator cuff is mobilized by releasing any adhesions on both the articular and bursal side. An "interval slide"—a complete longitudinal release of the rotator interval and coracohumeral ligament to the superior aspect of the coracoid—may be performed to improve tendon excursion [61,62]. A similar interval release can be performed between the posterior tendons to allow supraspinatus advancement. A satisfactory repair will allow the tendons to extend past the anatomic neck of humerus with the arm in a functional position of 10 to 15 degrees of forward flexion, abduction, and internal rotation. While no debridement of the tendon edge is required for rotator cuff healing, we perform minimal debridement of the cortical bone on the superficial aspect of the greater tuberosity before placing sutures [63–66]. Suture anchors or transosseous non-absorbable sutures are placed in the hard bone distal to the tuberosity utilizing a wide bridge of bone [67–70]. The insertion site may be augmented with a plastic or metal button in rare cases where the bone is of poor quality [71,72].

Deficient Rotator Cuff

Many procedures have also been proposed to augment a deficient rotator cuff. Although we strongly advise against rotator cuff debridement alone for "irreparable tears" due to the complication of anterosuperior humeral head migration, we do not advocate the routine use of allografts or synthetic grafts in this setting [73,74]. Instead, we have used partial repair of the rotator cuff with good success. Burkhart initially described this technique in fourteen patients with "irreparable" rotator cuff

tears, with the goal of restoring force couples and converting the defect to a functional cuff tear [75]. Complete coverage of the defect was not essential, and average residual defect size measured 2.9 square cm. With this technique, forward elevation improved from 59.6 degrees preoperatively to 150.4 degrees postoperatively. We have used a modification of this partial repair technique, leaving the posterolateral aspect of the head uncovered, with good success.

When the subscapularis tendon is deficient, transfer of the upper one-third of the tendon can be considered. However, Burkhart has recently demonstrated that this transfer may lead to superior migration of the humeral head by destabilizing force couples. We prefer partial repair to transfer of the subscapularis tendon, as even partial transfer of an intact subscapularis may further destabilize the shoulder and adversely affect active motion. Pectoralis major transfer may be used for a deficient subscapularis in rare cases [76,77]. Rockwood has reported successful transfer of the pectoralis major, pectoralis minor, or both in ten of thirteen patients with subscapularis deficiency. Resch has recently modified this technique, using a sub-conjoined tendon transfer of the pectoralis major, with good or excellent results in 9 of 12 patients.

In the case of posterior cuff deficiency where partial repair cannot be performed, transfer of either the latissimus dorsi or teres major tendons may be considered in rare cases [78,79]. Gerber performed latissimus dorsi transfer in 16 patients with irreparable rotator cuff tears and achieved restoration of 80% normal shoulder function in these patients. Range of motion in forward flexion improved from an average of 83 to 135 degrees. Poor outcome was associated with a deficient subscapularis tendon, and the authors advised against this transfer if the subscapularis is not functioning. With the tendon mobilization techniques described here and with the partial repair technique described by Burkhart, we have found few truly irreparable rotator cuff tears, and therefore have seldom had to utilize the latissimus or teres major tendon transfer for this indication.

Rehabilitation

While rehabilitation varies based on the size of the rotator cuff tear and the adequacy of repair, some general principles can be stated. In all cases, rehabilitation begins with passive-assisted range of motion exercises on the first postoperative day. Patients with small tears or no tears may begin pulleys on the first operative day, while, in patients with medium or large tears, pulley exercises are avoided for first 6 weeks in order to protect the cuff repair. Patients with large or massive tears undergo a modified Neer phase I protocol for 6 weeks that includes pendulum exercises, passive-assisted forward elevation to 140 degrees, and passive-assisted external rotation (supine) to 30 degrees.

Strengthening with isometric exercises is initiated at 6 weeks accompanied by active-assisted range of motion. Use of weights is avoided for at least 3 months in the rehabilitation period to avoid cuff re-tearing. Resistance exercises with light weights (1 to 3 pounds) can be initiated at 12 weeks, progressing to dynamic strengthening exercises at 6 to 8 months. Patients should be aware that full return of strength may require 12 to 18 months.

Results

While the results of rotator cuff repair vary depending upon the size of the tear and other patient factors, the results reported for arthroscopic, mini-open, and open techniques have been consistently successful for primary repairs. The results for arthroscopic repair are still being determined and there are currently no long-term studies evaluating their outcome. Two recent studies have found 84% and 92% good to excellent results for arthroscopic repair of full thickness rotator cuff tears. The results of mini open rotator cuff repair have also been excellent, with satisfactory results reported in 83% to 96% of patients [80–83].

The results of open repair for large to massive rotator cuff tears can be more variable depending on the size and chronicity of the tear. However, with close attention to the principles outlined in this chapter, we have found excellent long-term results for repair of large and massive rotator cuff tears. In a 7-year average follow-up study of 61 patients with repair of massive rotator cuff tears, 85% excellent or satisfactory results were achieved by Neer's criteria [20]. Also, 92% of patients had adequate pain relief and the ability to raise the arm above the horizontal. Only two re-tears occurred, and these were secondary to significant trauma.

A more recent study at the New York Orthopaedic Hospital of 231 shoulder massive rotator cuff tears demonstrated a 90% rate of satisfactory results with primary rotator cuff repair [15]. Function was improved postoperatively, with average active forward elevation 160 degrees, external rotation 55 degrees and internal rotation to T9. This represented an average improvement of 46 degrees elevation, 22 degrees external rotation, and internal rotation of 2 vertebral levels. External rotation power was improved from an average of 3.1 to 4.7. Satisfactory results were slightly less (76.5%) in patients with 4-tendon involvement. These results support the role of open primary rotator cuff repair for patients with large to massive rotator cuff tears.

Summary

While the pathophysiology of rotator cuff tendinopathy continues to be investigated, current management of rotator cuff disorders emphasizes traditional principles. Inflammation and bursitis are an important component of the pathology and initial management is focused on relief of these symptoms. The majority of patients will have satisfactory results with nonoperative management, including physical therapy and anti-inflammatory medication. The cause of rotator cuff tendinopathy remains unknown. Surgical management is directed at both relieving the subacromial impingement (extrinsic cause) and restoring continuity and function of the rotator cuff tendons (intrinsic cause).

With current operative techniques, rotator cuff repair can provide significant functional improvement and pain relief in the majority of patients. Important principles include performing anterior acromioplasty, bursal resection, rotator cuff mobilization, and tension-free repair to the greater tuberosity with nonabsorbable sutures. These principles are important whether the repair is performed through arthroscopic or open techniques. In cases of large or massive tears where the deltoid must be taken down, a meticulous deltoid repair must be performed, and the coracoacromial ligament should be repaired to prevent anterosuperior instability. Partial repair of the rotator cuff is recommended over performing transfer procedures. Postoperative rehabilitation requires avoidance of active exercises for 6 weeks and weights for 3 months. With these techniques, 84% to 96% satisfactory results can be expected.

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14
Tendinopathies Around the Elbow

Alan J. Johnstone and Nicola Maffulli

Introduction

During the last 20 years, there has been a better understanding of the underlying pathology of upper limb tendinopathies. This knowledge, coupled with a better understanding of the exact location of the pathology, has enabled surgeons to rationalize the use of existing nonsurgical and surgical management options, and to consider future therapeutic options. Not only has this approach improved the overall success of management, but it has also reduced patient morbidity. Research has also clarified the pathology and clinical presentation of a variety of disorders involving neighboring structures that can "mimic" symptoms commonly attributed to tendinopathies. These findings should reduce diagnostic error and help to identify causes of refractory symptoms. However, despite the advances made, the management of a significant proportion of patients with tendinopathies around the elbow remains a clinical challenge.

Tendon Injuries Around the Elbow

Tennis Elbow

Confusion exists in the literature as to what constitutes "tennis elbow," with some authors referring to lateral, medial, and posterior forms. However, most surgeons reserve this term to describe involvement of the lateral epicondyle, referring to the similar condition involving the medial aspect of the elbow as "golfer's elbow." Triceps tendinopathies are recognized as separate entities.

Etiology and Epidemiology of Tennis and Golfer's Elbow

Both tennis and golfer's elbow occur in patients aged between 35 to 50 years with a peak in the early 40s, although both conditions have been reported in teenagers and in patients in their 70s and 80s [1]. These conditions affect males and females equally, and most commonly involve the dominant arm [2]. In most patients, overuse of the limb gives rise to the symptoms with the severity being influenced by the overall intensity and duration of the activity. Characteristically, individuals, including competitive athletes, who place high demands on the upper extremities, are prone to developing epicondylopathy, although any task which involves repetitive activities may induce these conditions. Sports commonly associated with these conditions include racket sports, and sports which involve a throwing action resulting in eccentric loading of the muscles of the forearm. Other less common causes of epicondylopathy include a direct blow to the medial or lateral epicondyle. The symptoms may also ensue following a sudden extreme effort or activity resulting in injury. There also appears to be a group of patients susceptible to generalized tendinopathy: Nirschl referred to this group of patients as having a "mesenchymal syndrome," theorizing a possible genetic component giving rise to abnormal collagen formation [3]. These patients tend to have multiple problems that may include rotator cuff pathology, epicondylopathy, carpal tunnel syndrome, triggering of the long finger flexor tendons, and extensor tendon pathology such as de Quervain's disease. Interestingly, routine rheumatological investigations tend to be normal in this population, although more recently, Malmivaara *et al* have observed that a significant number of patients presenting with coexisting wrist and elbow tendinopathies have a higher incidence of rheumatoid factor positivity (31%) or human leukocyte antigen-B27 positivity (38%) compared with a control group [4]. This finding suggests a possible inflammatory component in the pathogenesis of the tendinopathy in some patients.

Pathology of Tennis Elbow

Despite the possibility of an inflammatory cause in some, in the majority of patients histology reveals a degenera-

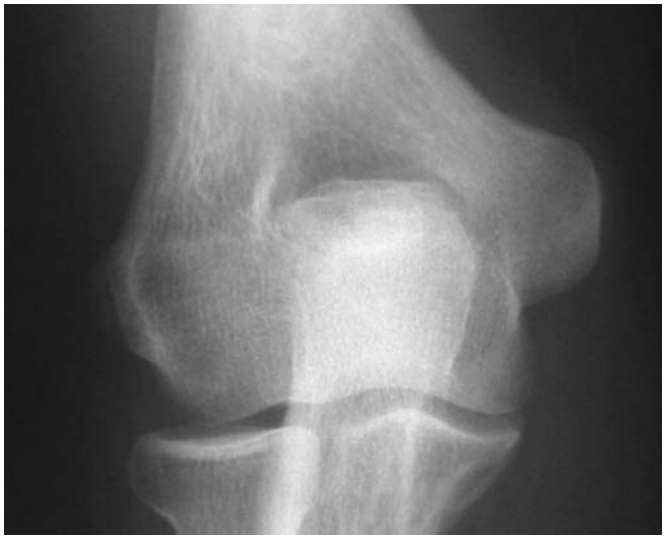

FIGURE 14-1. Calcification over the common extensor origin.

tive process within the tendon, and the histological appearances is remarkably similar to tendinopathy at other sites. Generally, the abnormal or pathological region of the tendon can easily be identified at surgery [2]. Characteristically, the abnormal region of the tendon is gray compared with the surrounding normal tendon, and may be slightly edematous [5]. It is also frequently friable, and may contain small flecks of calcification (Figure 14-1). Histology is consistent with disordered healing superimposed on a degenerative process, lacking the classical features of acute inflammation [6]. In particular, a granulation type of tissue containing fibroblasts is visualized and is referred to as "angiofibroblastic hyperplasia." Adjacent to this abnormal tissue, the neighboring tendon is hypercellular, containing histiocytes, lymphocytes, and occasional polymorphonuclear leukocytes, interspersed with small areas of localized degeneration.

Tennis Elbow

Tennis elbow affects approximately 1% to 2% of the population and is between 5 and 9 times more common than its medial counterpart [7]. Although any of the common extensor origin tendons can be involved, the extensor carpi radialis brevis tendon is the most commonly involved specific site [8]. Patients most commonly present with lateral elbow pain that frequently radiates into the extensor musculature of the proximal forearm. In most patients, symptoms relate to activities that stress the wrist extensor and supinator muscles, and especially to activities that involve forceful gripping or lifting of heavy objects. Clinical examination classically localizes tenderness to the anterior and lateral aspect of the epicondyle, and frequently over the distal part of the anterior aspect of the lateral condylar ridge [9] (Table 14-1).

TABLE 14-1. Main ethiopathogenetic hypotheses in tennis elbow (in chronological order)

Author	Year	Ethiopathogenetic hypothesis
Trethwan	1929	Synovial fringe inflammation
Cyriax	1939	Extensor carpi radialis brevis tear
Bosworth	1954	Hyaline degeneration of the annular ligament
Kaplan	1968	Neuritis of the radial nerve
Roles and Maudsley	1972	Radial nerve entrapment
Newman and Goodfellow	1975	Radial head fibrillation
Coel et al.	1993	Inflammation in the anconeus muscle

Patients with tennis elbow rarely experience significant tenderness over the posterior aspect of the epicondyle or condylar ridge, and if posterior tenderness is present, the clinician should consider other possible causes to explain the patient's symptoms. The resisted wrist extension test (Thomsen test) is useful, as is point tenderness increased with extension of the elbow while the wrist is held in full flexion and the forearm is pronated. However, reliance should not be placed upon the resisted middle finger extension test in differentiating between tennis elbow and compression of the posterior interosseous nerve [2]. One simple test, which can help to confirm the diagnosis at the outpatient clinic, is to inject local anesthetic around the site of maximal tenderness, usually the anterior aspect of the epicondyle or condylar ridge, or both sites depending upon the examination findings. A positive test will either temporarily abolish or significantly improve a patient's symptoms compared with the pre-injection findings. However, it is important to use a small volume of local anesthetic (2 to 3 mL) to reduce the risk of a false positive test.

Differential Diagnosis of Tennis Elbow

Although the majority of patients presenting with activity-induced lateral elbow pain have underlying degenerative changes within the common extensor origin, other causes of lateral elbow pain should be considered, especially if the clinical presentation is not typical of tennis elbow or if the patient's symptoms are resistant to appropriate conservative management. Narakas and Donnard suggested articular and neurogenic factors for lateral elbow pain in addition to tendinogenic causes [10]. The most widely accepted differential diagnoses include bursitis, stenosis of the annular ligament, inflammation of the synovium adjacent to the radial head, entrapment of the radial or posterior interosseous nerves, chondromalacia or early osteoarthritis of the radial head or capitellum, cervical nerve root entrapment, and laxity or instability of the lateral elbow ligament complex [2]. Generally, it is

possible to exclude these differential diagnoses clinically and, if necessary, by obtaining plain radiographs of the elbow. However, a detailed clinical and anatomical study documented entrapment of the posterior interosseous nerve co-existing in up to 5% of patients with tennis elbow [11,12]. This finding could in part explain why a significant proportion of patients fail to improve after apparently adequate conservative management. Entrapment of the posterior interosseous nerve should be considered if genuine weakness of the wrist extensor muscles can be demonstrated and if elbow pain is exacerbated by resisted supination of the forearm.

Investigations

It is usually possible to make the diagnosis of tennis elbow at the outpatient clinic. However, patients whose symptoms remain resistant to treatment may require further investigations to confirm the diagnosis, or, more commonly, to identify other causes of lateral elbow pain.

Plain Radiographs

Plain radiographs may be useful to identify intra-articular pathology, although calcification within the common extensor origin is seen in 22% of patients presenting with tennis elbow[13]. Soft tissue calcification frequently exists despite spontaneous resolution of elbow symptoms.

Thermography

This technique is rarely used clinically, although research has demonstrated that thermographic images correlate with clinical severity of symptoms, and may be of prognostic use [14].

High-Resolution Real-Time Ultrasonography

In experienced hands, ultrasonography can confirm the clinical diagnosis of tennis elbow, and provides additional information about the neighboring soft tissues and elbow joint [15].

Magnetic Resonance Imaging

The extent of tendon degeneration seen with magnetic resonance imaging correlates well with surgical and histological findings, and may have a place in the investigation of patients whose symptoms fail to resolve following apparently adequate management [16]. Despite this, magnetic resonance imaging is expensive, and is difficult to justify when one considers the high accuracy of clinical diagnosis.

Management of Tennis Elbow

The primary aim of management is to reduce or eliminate elbow pain that, in turn, will permit the patient to return to their chosen activities without limitation. Secondary aims include encouraging healing of the injured tendon and reducing the risk of recurrence of the condition.

Nonsurgical Management

Most studies document the overwhelming success of nonsurgical methods in the management of tennis elbow, with Nirschl reporting a personal success rate of 93% [13]. Unfortunately, recurrences are also common, especially if patients return to their previous level of activity without modification of the aggravating activity.

Many different nonsurgical approaches have been used to treat patients with tennis elbow. These include rest, activity modification, counterforce bracing of the extensor muscles of the forearm, eccentric exercise of the forearm extensor muscles, cryotherapy, therapeutic ultrasound, extracorporeal shock wave therapy, manipulation of the common extensor origin under general anesthesia, radiotherapy, acupuncture, nonsteroidal anti-inflammatory drugs, and injecting corticosteroids around the site of maximal tenderness [8]. It is unclear which of these nonsurgical methods are effective in the management of tennis elbow, with studies from different centres providing conflicting evidence about the benefits of ultrasound [17], and the use of nonsteroidal anti-inflammatory drugs [18]. Injected corticosteroids remain a mainstay in the management of tennis elbow, and are consistently helpful, although research has failed to confirm which corticosteroid preparation and dosage are most effective [8]. Similarly, the literature is unclear as to how many corticosteroid injections can be administered and to the timing of injections in view of the recognized complications of skin and subcutaneous fat atrophy combined with the potentially more serious complication of aggravating degeneration of the tendon. The mechanism of action of corticosteroids is also far from clear, since, in most patients, tennis elbow results from a degenerative process rather than from an inflammatory condition. Corticosteroids have a wide variety of effects on cells, and presumably their ability to limit intracellular activity by reducing the nuclear-cytoplasmic communication pathways influences the degenerative and reparative components of this condition. Irrespective of the nonsurgical method employed, modified rest is a fundamental part of the management that cannot be overemphasized. Similarly, modification of the aggravating activity is also of importance if the rate of symptomatic recurrence is to be reduced.

Surgical Management

Identifying which patients should be offered surgery is frequently difficult although, according to Nirschl, patients whose symptoms have continued for more than

TABLE 14-2. A chronological synopsis of some of the surgical procedures advocated in the management of resistant tennis elbow (in chronological order)

Franke (1910): Epicondylar osteotomy
Fisher (1923): Excision of the subcutaneous tissue
Hohmann (1927): Incision of the ECRB
Tavernier (1946): Partial lateral denervation
Bosworth (1955): Partial resection of the annular ligament
Kaplan (1959): Partial ventral denervation
Garden (1961): Distal lengthening of the extensor carpi radialis brevis
Wilhelm and Giesler (1962): Complete denervation
Goldie (1964): Excision of subcutaneous pathological tissue
Capener (1966): Decompression of the posterior interosseous nerve (supinator arcade)
Roles and Maudsley (1972): Decompression of the radial nerve
Boyd and McLeod (1973): Epicondylectomy and distal annular ligament excision
Wilhelm (1977): Radial nerve decompression (Hiatus of the radial nerve)
Posch (1978): Extensor fasciotomy
Narakas (1987): Proximal lengthening of ECRB and PIN decompression
Wilhelm (1989): Denervation and decompression of the posterior interosseous nerve

one year despite receiving a quality nonsurgical management regime should be considered for surgery [2]. He also suggests other criteria which indicate the severity of symptoms, such as radiographically visualized calcification within the soft tissues adjacent to the lateral epicondyle suggesting a refractory process; the need for multiple corticosteroid injections to control the level of symptoms; and the presence of constant pain without activity (Table 14-2).

A variety of operative procedures have been described, but perhaps the most important step has been the general agreement between surgeons that most cases of tennis elbow originate within the substance of the common extensor origin, with the extensor carpi radialis brevis being the most common specific site [8]. Open and percutaneous techniques have been described to release the common extensor origin ("extensor slide") and, regardless of the technique employed, they succeed in eradicating or significantly reducing symptoms in up to 90% of patients [8]. Open techniques also permit additional stages to be added to the release of the common extensor origin and include elevation of the extensor carpi radialis brevis muscle from the anterior aspect of the lateral condylar ridge, excision of the abnormal region of degenerative tendon, decortication of the lateral epicondyle and lateral condylar ridge to encourage revascularisation of the region, and selective denervation of the lateral epicondyle. However, there is concern about overzealous release of the common extensor tendon, as one may inadvertently release the extensor carpi radialis longus tendon, resulting in some postoperative elbow weakness, and approximation of the common extensor origin over the bone may limit this. Some surgeons divide the lateral collateral ligament as a routine part of their operation for the management of tennis elbow. However, this seems illogical due to the potential for causing elbow instability, which can itself give rise to significant symptoms.

Other operations have been described for the management of tennis elbow, but are less frequently employed. The procedure described by Bosworth is an extensive procedure, which addresses possible intra-articular pathology [19]. This technique involves the excision of part of the annular ligament in addition to releasing the common extensor origin. Such procedures still have their place provided the indications are strictly adhered to, but they have a higher morbidity than the less invasive procedures.

Postoperative Rehabilitation

Postoperative regimes vary significantly, but they all share certain common features, namely a period of rest followed by a period of gentle passive and active exercises during which time the patient is advised to avoid lifting heavy objects, forceful gripping of objects, and resisted dorsiflexion of the wrist and extension of the fingers. Most surgeons advocate a 6-week rehabilitation period for the majority of their patients.

Chronic Refractory Tennis Elbow Following Surgery

Some patients do not follow the prescribed postoperative regime and are left with residual symptoms, although in the majority of case, the severity of the residual symptoms does not warrant further surgery. However, difficulties arise when a patient continues to have severe symptoms despite undergoing apparently adequate surgery. Usually the first thing to consider is the time scale of their symptoms following surgery. Most patients should be treated nonsurgically for at least 6 to 9 months before any decision is taken to reoperate, unless it is obvious that another previously undiagnosed problem exists.

A detailed assessment of patients with refractory symptoms must be performed, taking into consideration any possible motives that they may have. Morrey describes two groups of patients; those whose symptoms are identical to their preoperative symptoms (Type I failure), and those patients who have different symptoms following surgery (Type II failure) [20]. He subclassifies the former group as follows: improper patient selection, incomplete or improper diagnosis, and inadequate or incomplete procedure. Correctly identifying patients who genuinely have symptoms and signs consistent with the diagnosis of tennis elbow and who are willing to comply

with the postoperative regimes is fundamental if the desired result is to be achieved following surgery. Therefore, the clinician must also assess a patient's motivation, and the possibility of secondary gain prior to offering surgery. Incomplete or improper diagnosis is self-explanatory. The most common cause for continuing symptoms is an undiagnosed entrapment of the posterior interosseous nerve that may be either the sole cause of a patient's symptoms, or coexisting with them, in approximately 5% of patients with tennis elbow [11,12]. Finally, patients may continue to experience symptoms if the surgical procedure performed did not fully address the underlying pathology. Type II failure is iatrogenic, and may result from overzealous surgery to treat tennis elbow. In particular, the surgeon should consider elbow instability, capsular pathology such as a capsular fistula or synovial herniation, and bursae as possible sources of symptoms. Arthrography is useful to identify capsular pathology, and some surgeons use arthroscopy to identify mild to moderate forms of ligamentous insufficiency, assuming that the pivot shift test and stress radiographs are negative.

Overall, potentially up to 85% of patients with continuing symptoms (types I and II) will improve, if a careful assessment of the presenting symptoms and signs, coupled with any necessary investigations are undertaken, so that the most appropriate secondary operation is performed [20].

Golfer's Elbow

Golfer's elbow is, rather confusingly, referred to by some surgeons as medial tennis elbow. In most patients, it results from overuse of the forearm wrist and finger flexor muscles, and in particular of the pronator teres and flexor carpi radialis muscles [7]. Occasionally, symptoms develop as a result of a direct injury to the medial epicondyle. In other patients, the causative factors may be difficult to identify, and this latter group of patients may fall into the "mesenchymal syndrome" category of patients. In most patients, the pathological changes observed within the common flexor origin mirror those seen with tennis elbow both macroscopically and microscopically. Essentially, the clinical examination findings are also very similar with localized tenderness being most evident over the anterior and medial aspects of the medial epicondyle and medial condylar ridge. Tenderness is frequently noted over the posterior aspect of the medial epicondyle and condylar ridge, and probably relates to the coexistence of ulnar nerve pathology which can be expected in up to 50% of cases [21]. The history provided by the patient is opposite to that of tennis elbow, with medial elbow discomfort being exaggerated by activities that involve active contraction of the wrist and finger flexors, and pronation of the forearm. In addition to localizing the site of maximal tenderness, the clinical diagnosis can also be aided by provocation tests that stress the muscle groups involved, such as resisted forearm pronation, and resisting wrist flexion. Increased point tenderness while extending the elbow with the forearm supinated and the wrist extended is also a useful clinical sign in my experience. Ulnar nerve entrapment is commonly associated with golfer's elbow, and it is therefore essential to palpate the course of the ulnar nerve from its emergence through the medial intermuscular septum, behind the medial epicondyle, and distally between the heads of flexor carpi ulnaris to identify localized tenderness. In addition, it is essential to assess the patient's hand and forearm for signs of sensory abnormalities, and more importantly for wasting and for weakness of the intrinsic muscles of the hand innervated by the ulnar nerve. These signs are frequently subtle.

Tinel's sign may also be useful in making the diagnosis of ulnar nerve entrapment when compared with the asymptomatic side. In approximately 10% to 15% of individuals, the ulnar nerve subluxes anteriorly with elbow flexion, and may "exaggerate" or even mimic the symptoms of golfer's elbow assuming that ulnar nerve pathology exists, or may even trick the clinician into assuming that the individual does not have coexisting ulnar nerve pathology due to the absence of tenderness posterior to the medial epicondyle [22]. Other diagnostic tests, such as the injection of a small volume of rapidly acting local anesthetic, are also useful in helping to confirm the diagnosis. Causes of medial elbow pain other than golfer's elbow are similar to those described for tennis elbow. However, instability of the ulnar collateral ligament complex is a particularly significant problem [2]. Typically, this happens to individuals who undertake activities that repetitively stress the ligament complex, such as throwing the javelin. These individuals should be investigated with stress radiographs, and possibly with arthroscopic assessment of elbow instability prior to surgical stabilisation.

Investigations

The diagnosis of golfer's elbow is essentially clinical although, on occasions, the investigations described for tennis elbow may be of use in assessing individuals with golfer's elbow. Nerve conduction studies assessing ulnar nerve damage may be of use to the clinician, especially if the surgeon anticipates that surgical decompression of the nerve is unlikely to significantly improve nerve function, and wishes to have the preoperative severity of nerve damage documented. This is particularly relevant when one considers that the long-term prognosis following release of the common flexor origin combined with decompression of the ulnar nerve strongly correlates with long-term ulnar nerve function[8].

Management of Golfer's Elbow

Approximately 90% of patients with symptoms and clinical findings suggestive of golfer's elbow without coexisting entrapment of the ulnar nerve can be treated successfully using the nonsurgical modalities described for tennis elbow [23]. The main significant complications reported following the injection of corticosteroids are the accidental intraneural injection of the ulnar nerve, and the injection of corticosteroid into the ulnar collateral ligament which may result in its rupture and elbow instability. To avoid accidentally injecting the ulnar nerve with steroid, corticosteroid injections should administered with the elbow in extension [22]. This precaution takes into account those patients (approximately 15% of the population) who have naturally occurring anterior subluxation of the ulnar nerve.

Surgery is reserved for those patients whose symptoms fail to improve following an adequate nonsurgical regime and for those with ulnar nerve symptoms and signs. Release of the common flexor origin is performed in a similar way to surgical decompression of the lateral aspect of the elbow. In many cases, abnormal degenerative changes are found within the common flexor origin, situated most commonly between the origins of the pronator teres and the flexor carpi radialis muscles. During this procedure care must be taken not to accidentally divide the ulnar collateral ligament which gives rise to considerable postoperative symptoms and frequently requires surgical reconstruction of the ligament complex. In view of the common association between ulnar nerve entrapment and golfer's elbow, decompression of the ulnar nerve is recommended while releasing the common flexor origin. For many surgeons, clinical findings or nerve conduction study evidence consistent with ulnar nerve entrapment is an indication for proceeding directly to surgical release of the common flexor origin combined with decompression of the ulnar nerve. However, opinions differ as to whether simple decompression of the ulnar nerve is sufficient, or whether this should be combined with anterior transposition. Kurvers and Vehaar suggest that anterior transposition provides better long term results compared with decompression of the ulnar nerve within the cubital tunnel [24]. However, one must consider the risk of damaging the neural vascular plexus by extensively mobilizing the ulnar nerve with its subsequent long-term problems [2].

Formal transposition of the ulnar nerve is unnecessary unless it naturally transposes with flexion of the elbow. Otherwise, wide decompression of the ulnar nerve proximally, distally, and at the level of the elbow is usually sufficient to reduce the tension on the nerve.

Triceps Tendon Injuries

Triceps Tendinopathy

This condition is observed almost exclusively in males undertaking regular heavy manual work and in throwing athletes[7]. It results from repetitive resistance of elbow extension resulting in a traction injury through the tendon's insertion into the olecranon. Clinical examination is usually sufficient to differentiate this condition from the considerably more common condition of olecranon bursitis, with the typical features of the former condition being direct tenderness of the olecranon and discomfort on attempting to extend the elbow against resistance. Although unnecessary, radiographs of the elbow usually demonstrate an olecranon traction spur (Figure 14-2). Management consists of avoidance of elbow extension activities for up to 6 months, and, in refractory cases, excision of the olecranon spur combined with repair of the triceps mechanism to the olecranon.

Rupture of the Triceps Tendon

Ruptures or avulsion injuries of the triceps tendon are rare, and occur in both men and women. Most injuries result from a fall on to the outstretched arm, combined with excessive contraction of the triceps in an attempt to break the fall. In 80% of cases, a small fragment of bone is avulsed from the tip of the olecranon and can be seen

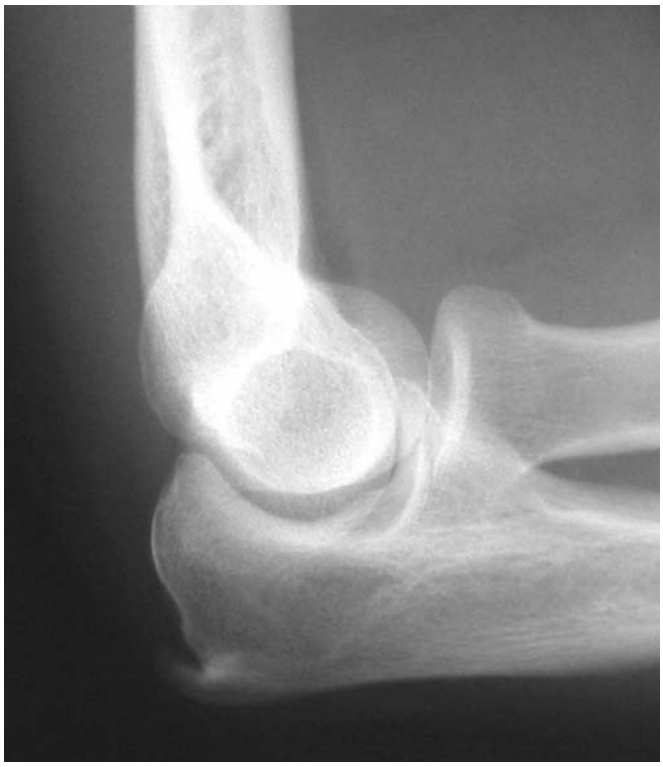

FIGURE 14-2. An olecranon traction spur.

readily on radiographs [25]. Physical examination may reveal a palpable defect depending on the extent of triceps retraction. Partial injuries are more difficult to identify, and may require to be confirmed using ultrasonography or magnetic resonance imaging.

The triceps squeeze test is useful in distinguishing partial tears from complete tears, and has features that resemble Simmonds test for assessing the integrity of Achilles tendon ruptures [26]. The arm is held in approximately 90 degrees of flexion, and the triceps muscle belly is squeezed. Extension of the elbow indicates a partial rupture of the triceps mechanism. Surgery is the management of choice for complete ruptures, permitting the tendon to be reattached to the olecranon via transosseous sutures. Some surgeons advocate the use of a flap of forearm fascia to augment the repair [25]. Postoperatively, the arm is immobilized at approximately 90 degrees of elbow flexion for 3 weeks and gently mobilized thereafter. Although few surgeons have extensive experience with these injuries, early repair appears to have a good outcome with excellent restoration of triceps function. Failure to repair the triceps tendon is associated with an inordinately high loss of elbow extension strength.

Spontaneous rupture of the triceps tendon, or rupture following minimal trauma has been observed in patients who have systemic disorders such as renal osteodystrophy, secondary hyperparathyroidism, Marfan's syndrome, and osteogenesis imperfecta tarda. Surgical repair is the management of choice, and augmentation of the repair with a strip of forearm fascia is indicated in most cases [26].

Distal Biceps Tendon Injuries

Unlike ruptures of the long head of the biceps in association with rotator cuff pathology, ruptures involving the distal biceps tendon are relatively uncommon and account for 3% to 10% of all biceps tendon injuries [27]. By far the most common site for injury to the distal tendon is at its point of insertion into the radial tuberosity. Characteristically, this injury occurs predominantly in males (greater than 95%) and usually occurs during the fourth through to the sixth decades of life [7]. Not uncommonly, younger patients with distal biceps tendon ruptures present after using anabolic steroids as part of a bodybuilding regime [8]. This injury results from an eccentric contraction of the biceps while lifting heavy loads, and is often accompanied by a popping sensation in the anterior aspect of the elbow in addition to severe pain. Profound weakness of elbow flexion and supination of the forearm, combined with pain while performing these activities against resistance, are in keeping with the clinical diagnosis. In addition to identifying localized tenderness over the anterior aspect of the elbow and over the radial tuberosity, a palpable defect in the line of the biceps tendon is frequently felt, although the presence of an intact lacertus fibrosis can make the clinical diagnosis slightly harder.

Investigations to confirm the diagnosis are rarely required, except on rare occasions when the distal biceps tendon is partially torn, or in preoperative assessment of chronic ruptures where magnetic resonance imaging has been used to identify the level of the proximal end of the biceps tendon within the arm [28]. Plain radiographs, although not essential for making the diagnosis, sometimes reveal hypertrophy of the radial tuberosity indicative of an ongoing degenerative process prior to rupture of the distal biceps tendon, but add little to the diagnosis or to planning management.

Partial ruptures of the distal biceps tendon do occur, but are much less common than complete ruptures. Although these injuries have been categorized according to the anatomical site of the lesion, most of partial biceps tendon injuries occur at the point of insertion into the radial tuberosity, and, when diagnosed, should be treated in a similar manner to the far more common complete biceps tendon rupture, assuming that most partial ruptures herald an impending complete rupture. The other sites for partial injury of the distal biceps include the musculotendinous junction, which is very rare, and a tear of the biceps tendon in continuity, which is also uncommon. Due to the rarity of the latter two types of partial rupture, the literature is far from clear as to how they should be treated, although some advocate augmenting the site of injury with a tendon autograft or allograft, or by using a ligament augmentation device at the time of surgical repair.

Management of Distal Biceps Tendon Ruptures

As mentioned, the most common site for injury of the distal biceps tendon is at its insertion into the radial tuberosity. Complete ruptures at this site are considerably more common than partial ruptures, and the literature strongly suggests that both injuries should be treated surgically if reasonable long-term function is to be restored [26]. Nonsurgical management of these injuries results in up to 40% to 50% loss of elbow flexion strength and forearm supination strength[7]. In addition, it is advisable to proceed with surgery within two weeks of sustaining the injury to obtain the best results, before the tendon retracts proximally. Two surgical exposures have been well described: the anterior Henry approach to the elbow and proximal forearm, and the two incision technique popularized by Boyd and Anderson [29].

The main advantage of the procedure undertaken using the anterior Henry approach is that only one incision is required, and may be extended as necessary to improve the access to the radial tuberosity. However, this

approach is technically more demanding than the two-incision approach, and there is greater risk of damaging the posterior interosseous nerve. The two incision technique is easier to perform and uses two limited incisions, to first identify the distal end of the biceps tendon, and, through a simple muscle-splitting incision placed over the radial tuberosity with the forearm held in full pronation, obtain access to it. Surgeons undertaking the two incision technique should be aware of the dangers of inducing ectopic bone formation between the proximal radius and ulna by accidentally exposing the radial side of the ulna. To avoid this complication, which in some patients has resulted in synostosis, it is important to maintain the plane of muscle dissection adjacent to the radius, while passing the tendon around to the posterior aspect of the forearm, which in turn will prevent inadvertent stripping of the anconeus muscle from the radial aspect of the ulna [26]. Irrespective of the surgical approach employed, the biceps tendon is attached to the radial tuberosity after hollowing out the tuberosity to accommodate the tendon, using burrs or a curette. The tendon can be attached with transosseous sutures placed at the lip of the tuberosity, or, more recently, with suture anchors. Postoperatively, the patient's elbow should be splinted at 90 degrees of flexion for 3 to 4 weeks. Some surgeons advocate a period of dynamic splintage for 4 to 6 weeks thereafter, which permits active extension. Alternatively, patients are permitted to actively extend the elbow while passively flexing the joint. Thereafter the patient is encouraged to actively flex and extend the elbow in addition to actively rotating the forearm. It is not recommended that patients be permitted to return to full activity for 6 months after surgery. From the literature, normal strength is not achieved following surgical repair in a considerable number of patients, with poorer results being more common following surgery to the non-dominant arm [8]. In addition, a considerable proportion of patients lack a full range of flexion and forearm supination, although patients' satisfaction is generally high. However, the results of patients treated surgically compare very favorably with patients treated nonsurgically.

Delayed Surgical Management of Distal Biceps Tendon Ruptures

In some instances, the diagnosis of biceps tendon rupture is either made late or the decision to operate is deferred for other reasons. The ideal time to undertake surgical repair is within 2 weeks of the injury, during which time the biceps tendon can be easily retrieved and mobilized, although there have been reports of successful tendon retrieval being undertaken up to 3 months following injury. Where excessive scarring is present, it may prove impossible to mobilize the tendon sufficiently to permit direct repair to the radial tuberosity, and tendon autografts, sometimes strengthened with a ligament augmentation device, have been used successfully [8]. Another alternative is to attach the stump of the biceps tendon to the brachialis muscle which improves elbow flexion strength, but has no effect on supination strength.

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15
Hand and Wrist Tendinopathies

Graham Elder and Edward J. Harvey

Introduction

More than half of all occupational disorders can be attributed to chronic tendinous pathologies [1]. A large percentage of these involve the hand and wrist, and constitute a significant economic burden to society. The risk of hand and wrist tendinopathy in patients who perform highly repetitive and forceful jobs is 29 times greater than in patients who perform jobs that are low in repetitiveness and force [2]. A number of terms have been used to categorize wrist and hand tendon disorders in the literature, including overuse injury, repetitive strain injury and, more recently, cumulative trauma disorder (CTD). These terms reflect a common presumed etiology based on repetitive loading leading to tendinopathy and/or tenosynovitis. Chronic tendon disorders are also frequently seen in various sporting activities, both at professional and amateur levels. Racquet sports in particular are commonly associated with wrist and hand tendinopathies [3,4]. Other sports commonly associated with wrist tendinopathies include golf, weightlifting, gymnastics, and bicycling [3,4,5].

Because of the complex organization of tendons about the wrist and hand, reaching an exact diagnosis can be difficult. This chapter has been arranged by anatomical site in order to contrast diagnoses. Common differential diagnoses for each region are presented in tabular form (Table 15-1). Regardless of the etiology, chronic tendon disorders generally respond to nonoperative management, but frequently require lengthy treatment with unpredictable outcomes. The initial course of nonoperative treatment is generally the same regardless of anatomical site. Surgical intervention in tendon pathology can present important technical challenges. The authors' preferred surgical approach will be discussed in detail within each anatomical subsection.

Diagnostic Approach

As with the evaluation of any musculoskeletal disorder, a thorough history and physical examination is essential. This is followed by selective anesthetic injections (often the best diagnostic test) and by imaging when necessary. Particularly important in hand and wrist tendinopathies is the precise definition of the exact location of pain. In acute pathology, patients can frequently localize the area of most significant pain with one finger and this can be the most important diagnostic clue (Table 15-1). In chronic situations, the pain becomes more diffuse, and accurate diagnosis becomes more dependent upon provocative testing and selective anesthetic injections. The role of magnetic resonance imaging (MRI) and ultrasound is still controversial, although, in selected cases, both of these imaging techniques can be important for accurate diagnosis.

Nonoperative Management

As with chronic tendon disorders in other parts of the body, nonoperative therapy is almost always the initial management of choice in hand and wrist tendon disorders. This may include rest, with limitation of the inciting activity, part-time immobilization using removable splints, complete immobilization using casts or, more commonly in the hand and wrist, nonremovable orthoses. Nonsteroidal anti-inflammatory drugs (NSAIDs) may play a role, but should be used with caution when the inciting event is not discontinued (in a professional athlete or laborer), as their analgesic effect may allow increased mechanical loading, leading to rupture. Physiotherapy offers both acute anti-inflammatory management (ice, ultrasound, and electrical modalities) and long-term proprioceptive rehabilitation, which may play a role in

Table 15-1. Differential diagnosis of wrist pain

Site of maximal wrist pain	Common differential diagnoses
Dorsoradial	1. De Quervain's tenosynovitis (1st extensor compartment) 2. Intersection syndrome (2nd extensor compartment) 3. EDB manus syndrome
Middorsal	1. Dorsoradial ganglion 2. EPL tenosynovitis (3rd extensor compartment) 3. EIP tenosynovitis (4th extensor compartment) 4. EDC tenosynovitis/4th extensor compartment syndrome
Dorsoulnar	1. ECU stenosing tenosynovitis (6th extensor compartment) 2. ECU recurrent subluxation/dislocation (6th extensor compartment) 3. EDM stenosing tenosynovitis (5th extensor compartment)
Volar-radial	1. De Quervain's tenosynovitis (1st extensor compartment) 2. OA of 1st CMC joint 3. Ganglia 4. Scaphoid cysts/fracture 5. FCR tendinopathy 6. Linburg's syndrome
Midvolar	1. Carpal tunnel syndrome 2. Linburg's syndrome
Volar-ulnar	1. FCU tenosynovitis 2. Guyon's canal syndrome 3. Pisotriquetral arthritis

secondary prevention. Steroid injections of tendon sheaths remain an effective form of treatment, although controversy continues to exist regarding their safety and the number and frequency of injections [6]. The effects of direct intratendinous injection of corticosteroids have not been scientifically studied, and such treatment can therefore not be recommended.

Once the patient is asymptomatic (whether by operative or nonoperative means), a period of rehabilitation emphasizing proprioception and controlled activity simulation prior to returning to full activity is essential. Recurrence of the tendinopathy can be common if this part of the treatment protocol is ignored. For laborers, a work hardening program involving occupational therapy might be considered.

Dorsal-Radial Wrist Pain

1. De Quervain's Tenosynovitis

Described in 1895 by de Quervain, this tendon disorder involves both the extensor pollicis brevis (EPB) and the abductor pollicis longus (APL), which originate from the middorsal aspect of the radius and ulna. They travel through a fibro-osseous tunnel (first dorsal extensor compartment) and form the radial border of the anatomical snuffbox. The APL inserts at the base of the first metacarpal, and the EPB inserts at the base of the first proximal phalanx. Both cadaveric and surgical dissections have demonstrated significant variations in the anatomy of the first extensor compartment. Further division within the fibro-osseous tunnel by a septum has been noted in 34% to 60% of cases [7–10]. This septum effectively creates a separate compartment for the EPB tendon within the first dorsal extensor compartment, and plays an important role in the effectiveness of steroid injections and surgical release. The APL has been noted to have more than one tendinous slip (usually 2 to 4) in 58% to 94% of dissections, while the EPB is almost always represented by a single tendon [7–10].

Despite the anatomic variations, the clinical presentation is fairly characteristic. The classic triad consists of tenderness over the radial styloid, swelling over the first extensor compartment, and a positive Finkelstein's test. More specifically, the patient usually presents with a complaint of pain of insidious onset localized over the radial styloid and exacerbated by wrist or thumb movement (usually ulnar deviation). The symptoms are often present for many months prior to seeking medical attention. If the condition is related to athletic activity, it is most commonly associated with golf, racquet sports, and fly fishing [3]. Swelling along the course of the first extensor compartment is inconsistent. Tenderness over the retinaculum is constant [11]. Extensor triggering or locking, demonstrated by a palpable and sometimes audible "click" with active extension of the thumb, is an uncommon (prevalence of 1.3%) but recognized component of long-standing stenosing tenosynovitis [12].

Objectively, the most reliable sign is Finkelstein's test, although it can be negative when the EPB alone is involved [11]. The test is performed *passively* by deviating the wrist ulnarly with the thumb lying along the palmar aspect of the index lightly clenched within the fingers. Clenching the thumb too tightly causes pain even in normal wrists [13]. Finkelstein's test reproduces the patient's symptoms, with pain along the first extensor compartment. Resisted thumb extension can also provoke the symptoms but is a less reliable test. In difficult cases, ultrasonography has recently been reported as a reliable method of diagnosing de Quervain's tenosynovitis [14]. The differential diagnosis includes intersection syndrome, which usually presents with pain more proximally (see Intersection Syndrome).

Provocative test: Finkelstein's test (see text).

Management

Nonoperative treatment is generally successful. In particular, steroid injection into the tendon sheath is the preferred initial treatment, with an 80% success rate [15]. Failure of steroid injection is usually associated with the existence of a septum forming a separate EPB subcompartment. Steroid injections can be repeated up to 3 times. Failure at this point is an indication for operative release, which is generally successful. Extensor triggering is a relative indication for operative decompression, as nonoperative intervention, including steroids, has poor results [12].

Decompression can be performed through a transverse or longitudinal incision over the first extensor compartment at the level of the radial styloid. Care must be taken to avoid traction on the dorsal radial sensory nerve. The compartment is released on the dorsal aspect to prevent volar subluxation of the tendons with thumb motion. It is important to accurately identify all slips of the APL tendons and to completely divide any septations creating EPB subcompartments. Complications of this procedure include injury to the dorsal radial sensory nerve, volar tendon subluxation, hypertrophic scarring, tendinous adhesions, and persistence of symptoms due to incomplete decompression (missed subcompartments). Postoperatively, a thumb spica is used for 2 to 3 weeks before beginning rehabilitation. Inciting activities are restricted for another 6 weeks or until rehabilitation is completed.

2. Intersection Syndrome

Intersection syndrome presents with pain and swelling localized to the dorsum of the distal forearm, approximately 4 to 6 cm proximal to the wrist. In this area, the abductor pollicis longus (APL) and extensor pollicis brevis (EPB) intersect the extensor carpi radialis brevis (ECRB) and longus (ECRL) (see Figure 15-1). The basic pathology is thought to result from friction at this intersection point between the muscle bellies and tendons, leading to tendinopathy and/or bursitis. The exact pathoanatomy of the intersection syndrome remains elusive, thus explaining the plethora of terms used to describe it including abductor pollicis longus bursitis [16], crossover tendinitis, squeaker's wrist, and peritendinitis crepitans [17].

A high index of suspicion is the key to diagnosis. Symptoms occur after prolonged repetitive activity, usually involving flexion and extension of the wrist with eccentric loading of the extensor compartment (e.g. hammering). Although predominantly seen in the work environment, certain athletic activities can lead to intersection syndrome. "Bugaboo forearm" in deep-powder helicopter skiers has recently been described, resulting from repetitive extension and radial deviation of the wrist against the resistance of deep snow on withdrawal of the planted pole [18]. Racquet sport players [19] and oarsmen [17] are also vulnerable to this condition. In addition to localized pain and swelling, crepitus is sometimes palpable (and audible) with flexion and extension of the wrist. This is pathognomonic of the syndrome. Weak pinch and diminished grasp may also be seen. The differential diagnosis includes de Quervain's tenosynovitis, which presents with pain and swelling more distally in the first extensor compartment [20,21]. The Finkelstein's test may be positive in patients with intersection syndrome, but the pain experienced is more proximal, in contrast to de Quervain's tenosynovitis, where the pain is in the first extensor compartment (Figure 15-1A).

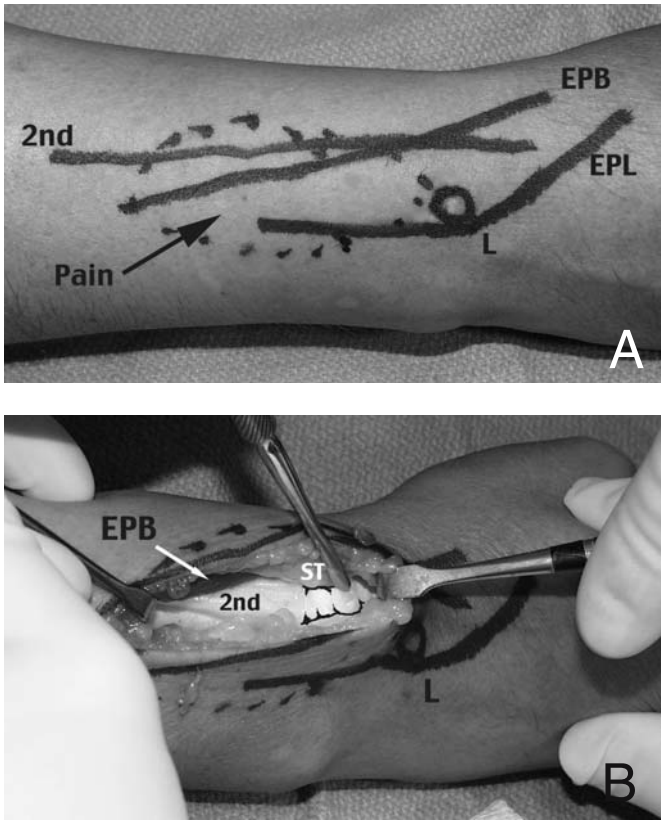

FIGURE 15-1. (A) A 44-year-old janitor with long-standing dorsoradial wrist pain exacerbated by daily activity. Failure of treatment with braces and multiple injections for de Quervain's tendinitis brought the patient for another opinion. Note that the pain, described as burning and crepitus, is more proximal and dorsal than normal for de Quervain's (as indicated by dark arrow and dotted lines). (B) At surgery, the EPB (white arrow) is reflected from the second compartment. There is an area of stenosis (ST) in the second sheath just proximal to Lister's tubercle (L). Release of this stenotic area allowed early return to manual labor.

Provocative test: Direct pressure at the point of intersection producing pain and crepitus with flexion/extension of the wrist.

Management

Appropriate nonoperative management will yield complete and permanent relief in 60% of patients [22]. Failing this, there are two schools of thought regarding appropriate surgical intervention. The standard operative decompression involves a longitudinal incision over the site of maximum swelling at the point of intersection in line with the APB and EPB muscle bellies [17]. The fascia and sheath around the APB and EPB are then released. This approach directly addresses the site of symptomatology, namely the point of intersection. Williams [17] described operative results in 11 athletes (mostly rowers) who underwent standard decompression at the site of intersection between 2 weeks and 18 months from onset of symptoms. All patients had excellent results, with resumption of normal activities and return to full athletic training within one week. There were no recurrences up to 4 years postsurgery.

Grundberg and Reagan [22] have described an alternative intervention based on operative findings in 13 patients. They propose that the basic pathology involves tenosynovitis of the second extensor compartment (ECRB and ECRL) causing referral of pain and swelling more proximally. A similar presentation is noted in carpal tunnel syndrome secondary to flexor tenosynovitis, with pain and swelling localized in the distal aspect of the forearm. These authors reported complete relief of symptoms in all 13 patients by decompressing the second compartment, thus confirming their hypothesis. No intervention was performed more proximally at the site of intersection. Persistent symptomatology in 2 of the 13 patients who had undergone previous operative intervention more proximally was relieved by decompression more distally of the second compartments, thus further supporting their hypothesis. Operative intervention involving decompression of the second extensor compartment resulted in 100% relief of symptoms at an average 10 months follow-up. All patients returned to their previous employment [22].

Our operative technique involves a longitudinal incision in line with the radial wrist extensors extending from the wrist joint proximal to the swollen area. Incision of the fascia reveals the swollen APB and EPB. The EPB muscle belly is released to expose the second compartment. Only upon decompression of the second compartment significant tenosynovitis of the ECRB and ECRL is seen (see Figure 15-1). The wrist is then immobilized in a plaster forearm splint for 10 days. The inciting activity should be avoided for at least 12 weeks postoperatively.

3. Extensor Digitorum Brevis Manus Syndrome

The extensor digitorum brevis manus (EDBM) muscle is a rare aberrant muscle found on the dorsum of the hand that is frequently confused with a ganglion or a tumor [23]. The incidence of the EDBM muscle is 1.1% to 3.0% based on cadaveric dissections of 3404 and 559 hands, respectively [21,23]. Its anatomy and phylogeny are controversial. Ogura et al. suggest that the EDBM muscle is a variant of the extensor indicis proprius (EIP) muscle [23]. Riordan et al. point out that the muscle probably represents a homologue of the extensor digitorum brevis of the foot. Still others maintain that it is a derivative of the dorsal interosseous musculature [24].

Ogura et al. dissected 559 hands [23]. The EDBM originates from the distal radius and its periosteum, or from the radiocarpal ligament in some cases. Gama et al. [21], on the other hand, dissected 3404 hands and found its origin to be the wrist capsule beneath the dorsal carpal ligaments at the level of the scaphoid, lunate, capitate, or hamate, or occasionally at the level of the distal radial epiphysis. The insertion is usually on the ulnar side of the extensor mechanism at the level of the metacarpophalangeal (MCP) joint of the index finger. In some cases, it also inserts on the radial side of the long and ring finger [24]. The EDBM muscle is innervated by the posterior interosseous nerve that also supplies sensation to the dorsal wrist capsule. The EDBM muscle may hypertrophy through heavy use of the hand, leading to compression of the muscle belly against the distal edge of the extensor retinaculum [24–26]. Symptoms likely result from the associated synovitis.

The key to diagnosis of the syndrome is an awareness of its existence. It should be noted that presence of an EDBM muscle is usually not symptomatic, and patients may present because of an unusual painless mass, which should prompt an evaluation as mentioned below. There may be a hereditary component [24,27]. When it is symptomatic, patients are usually heavy laborers and present with dorsoradial or middorsal wrist pain and swelling during or after excessive use of the affected hand. Physical exam reveals an easily identifiable fusiform mass, usually on the proximal second metacarpal space. The mass is soft, freely mobile, and usually nontender, unless there is significant associated synovitis. It becomes firm when the wrist is slightly flexed and the fingers are fully extended [23]. Resisted extension of the fingers reproduces the pain [21], as does pressure on the palm of the hand against a table with the wrist in full extension [23]. The mass does not transilluminate nor fluctuate. Radiographs are usually normal, and aspiration is negative. The differential diagnosis includes ganglions, tenosynovitis, synovial cysts, exostosis, and carpal bossing [28–30]. Diagnosis can be aided with electromyography [23].

Provocative test: Pressure on palm of hand against table with wrist in full extension

Management and Results

If the diagnosis from the clinical exam and EMG studies is certain, then no treatment is necessary for a painless EDBM muscle mass other than reassurance for the patient. When the diagnosis is in doubt, however, MRI can be utilized. If the EDBM muscle is identified, then no intervention is necessary. If identified at surgery, the muscle is left in situ as a useful finger extensor.

For symptomatic EDBM syndrome, a trial of nonoperative therapy is warranted, including NSAIDs, corticosteroid injections, and splinting. Failure will frequently lead to operative release. A simple release of the extensor retinaculum through a dorsal approach may be effective, although recurrence of symptoms necessitating reoperation to excise the muscle has been documented [26,28]. When excising the EDBM muscle, attempts to leave the EIP tendon intact should be made [23]. Exploration for coexisting ganglions should also be undertaken, as 25% of EDBM syndromes are associated with ganglions [23,25].

Middorsal Wrist Pain

1. Extensor Pollicis Longus Tenosynovitis

Extensor pollicis longus (EPL) tenosynovitis is most commonly seen in patients with rheumatoid arthritis. In athletes, it is generally related to racquet sports. A nonrheumatic form can occur after distal radius fractures when fracture fragments cause impingement of the EPL tendon. Early diagnosis in this case is important to prevent rupture at the level of Lister's tubercle.

The EPL originates from the posterior surface of the middle one-third of the ulna and interosseous membrane, and passes just ulnar to Lister's tubercle through the third extensor compartment, where it makes an acute angle before inserting on the posterior surface of the base of the distal phalanx of the thumb. Two anatomic variations that may contribute to EPL tenosynovitis have been noted in cadaveric dissections by Morgensen and Mattson. First, the thickness and length of the septum between the third and fourth compartments is quite variable when compared to the septum between the second and third compartments. Second, the distance between the EPL musculotendinous junction and the proximal edge of the extensor retinaculum varies from 12 to 25 mm (thumb in neutral) with one-quarter of the junctions ending within the extensor sheath [6].

The patient generally presents with a several-months history of dorsal wrist pain, swelling, and occasionally crepitus at the level of Lister's tubercle. There is usually no specific traumatic event, although the patient may relate the symptoms to a new sporting activity or a repetitive maneuver at work. Upon examination, there is tenderness and swelling along the EPL tendon, particularly at Lister's tubercle. The pain is reproduced at the level of the wrist with active and resisted thumb extension. Passive flexion of the thumb interphalangeal (IP) joint can also reproduce pain along the EPL sheath. Severe cases of EPL tenosynovitis may present with triggering of the thumb IP joint with active motion.

Patients with EPL ruptures after distal radius fractures usually present several months to years after the trauma complaining of acute inability to fully extend the thumb associated with pain along the tendon sheath at the level of Lister's tubercle [32]. Lateral radiographs of the wrist or computed tomography (CT) scans help to delineate bony pathology that may be amenable to simple excision. *Provocative test:* Reproduction of pain with resisted thumb extension.

Management

Nonoperative management including steroid injection and splinting is usually successful, although some authors recommend that steroids be used with caution, as increased local tissue pressure may increase the risk of tendon rupture [33,34]. For chronic nonresponsive cases, operative decompression is indicated. There are 4 reported operative cases in the English literature in 3 articles [6,31,36]. All 4 cases resolved with surgical release, one of which remained symptom free at 10 year follow-up. The extensor retinaculum is often thickened with a stenotic indentation visible in the underlying swollen EPL tendon. There are two operative techniques. In the first [6], a standard longitudinal incision is made over the third extensor compartment retinaculum. The septa between the third and fourth as well as second and third compartments are released. The extensor retinaculum is closed over the EPL to prevent bowstringing.

We prefer the second technique, in which a longitudinal incision is made centered on Lister's tubercle. The EPL tendon is completely released and simply transposed to the underlying subcutaneous tissue. The extensor retinaculum is then closed to prevent relocation of the EPL tendon. In our experience, as well as in that of other authors [36], bowstringing has not been a problem with this technique. It may require an extended period before the patient returns to baseline function.

Treatment of an acute degenerative rupture is either benign neglect or a tendon transfer from the extensor indicis proprius (EIP) to the remnant of the EPL, depending on the patient's activity requirements. Primary repair is usually impossible due to the chronic degenerative nature of the rupture. In the prerupture phase where

a bony prominence is seen on lateral radiographs, consideration should be given for an exostosectomy. This may prevent complete attenuation of the tendon and reverse the degenerative process, relieving pain and swelling.

2. Extensor Indicis Proprius Syndrome

The extensor indicis proprius (EIP) originates from the dorsal aspect of the distal third of the ulna and the adjacent interosseous membrane. After passing through the fourth extensor compartment deep to the extensor digitorum communis (EDC), it inserts on the dorsoulnar expansion of the index EDC. The musculotendinous junction lies predominantly within the confines of the fourth dorsal compartment. Anatomical studies further noted this compartment to become extremely tight when the wrist was held in flexion as the bulky musculotendinous portion of the EIP muscle passed under the proximal edge of the extensor retinaculum [37]. Repetitive irritation of the tenosynovium as the EIP junction passes under this proximal retinacular edge is felt to initiate the syndrome. Hypertrophy of the EIP with athletic training is also considered a contributing factor [37].

The patient presents with point tenderness and swelling over the middorsal aspect of the wrist corresponding to the fourth compartment and the EIP musculotendinous junction. The symptoms are commonly noted after repetitive activity involving wrist flexion and extension. The provocative maneuver begins with the wrist in maximum pain-free flexion. The examiner resists active index extension with pressure on the proximal phalanx. The patient will describe a sudden pain localized to the ulnar aspect of Lister's tubercle just distal to the extensor retinaculum [43]. The differential diagnosis includes EDC tenosynovitis, EPL tenosynovitis, dorsoradial ganglion, and Kienbock's disease.

Provocative test: Resisted index extension with the wrist in full flexion.

Management

Nonoperative management (including rest, splints, and local corticosteroids) is usually successful. If this fails, surgical decompression is indicated. The literature to date provides only sporadic case reports describing operative intervention. Spinner et al. documented 3 patients with persistent symptoms after failing conservative management. All 3 responded to surgical release. Ritter et al. performed surgical release on 2 patients, both of whom returned to full, unrestricted activity, remaining pain free at 1- to 2-year follow-up. This is performed through a middorsal longitudinal incision over the ulnar aspect of the fourth compartment. Typically, the muscle belly of EIP extends into the fourth compartment with marked synovitis surrounding both the tendon and the muscle [37].

3. Extensor Digitorum Communis Tenosynovitis and Fourth-Compartment Syndrome

Extensor digitorum communis (EDC) tenosynovitis is exceedingly rare. It is suspected when a patient presents with diffuse pain over the fourth extensor compartment that is aggravated by passive wrist and finger flexion. Triggering is generally not seen [40]. Pain may be reproduced with resisted finger and wrist extension. EIP syndrome must be ruled out using appropriate provocative maneuvers. (See the EIP section.)

Provocative test: Diffuse pain with resisted finger and wrist extension.

Management

It is frequently very difficult to identify the exact source of the pathology, and a global therapeutic treatment program targeting dorsal wrist pain must be instituted [41,42]. Failure to respond to nonoperative measures should raise suspicion of an anatomic abnormality that must be addressed with surgical exploration and possible release of the fourth extensor compartment [43,44]. Hayashi et al. [39] have recently proposed a theory which they have termed "fourth-compartment syndrome." They describe several pathological conditions (including EDC tenosynovitis, muscle anomalies, carpal bone anomalies, and occult ganglion) that can increase pressure within the fourth extensor compartment, ultimately compressing the posterior interosseous nerve (PIN) directly or indirectly causing dorsal wrist pain. Surgical decompression releases the pressure on the PIN eliminating wrist pain.

Dorsal-Ulnar Wrist Pain

1. Extensor Carpi Ulnaris Tenosynovitis

Extensor carpi ulnaris (ECU) tenosynovitis is the second most common wrist tendinopathy seen in sports, and is particularly associated with rowing and racquet sports [3]. The ECU originates from the common extensor origin on the lateral epicondyle as well as the posterior one-third of the ulna and inserts at the base of the fifth metacarpal after traversing the sixth extensor compartment. ECU is the only extensor that has its own fibro-osseous tunnel that is not made up of the extensor retinaculum [38]. This tunnel overlies 1.5 to 2 cm of the distal ulna. The ECU is held within this groove by its tendon sheath.

Patients present with a history of chronic pain localized to the dorsal-ulnar aspect of the wrist just distal to the dorsum of the ulna. There is frequently associated swelling and "thickening" in this area. Sometimes there is a history of trauma, but usually the pain is of insidious onset. Examination reveals tenderness over the ECU tendon and ulnar head. Pain is increased with resisted wrist ulnar deviation combined with extension. Local injection is usually diagnostic. The differential diagnosis includes ECU subluxation/dislocation, extensor digiti minimi (EDM) tenosynovitis, and triangular fibrocartilage complex (TFCC) disorders.

Provocative test: Resisted wrist ulnar deviation and extension.

Management

A standard nonoperative approach will yield satisfactory results in most cases. Hajj et al. [44] describe 3 cases of ECU tenosynovitis that failed conventional nonoperative treatment requiring surgical release of the sixth extensor compartment. All 3 patients had complete relief of symptoms at an average 16 months follow-up, with return to full activity. Crimmins and Jones [45] performed a retrospective review of 15 patients with 10 to 14 months follow-up. Seven of 15 patients failed conservative therapy consisting of splinting and steroid injections. Six of these 7 had good or excellent results with surgical release. Surgical release of the sixth compartment is the treatment of choice if conservative management fails. This is performed through a longitudinal incision over the sixth extensor compartment. The thickened fibro-osseous canal is released on the radial side of the sixth compartment, allowing tight repair of the extensor retinaculum to prevent residual subluxation of the ECU postoperatively [44] (see Figure 15-2). The wrist is then immobilized for 2 to 3 weeks postoperatively in a volar-based splint with 20 degrees of extension.

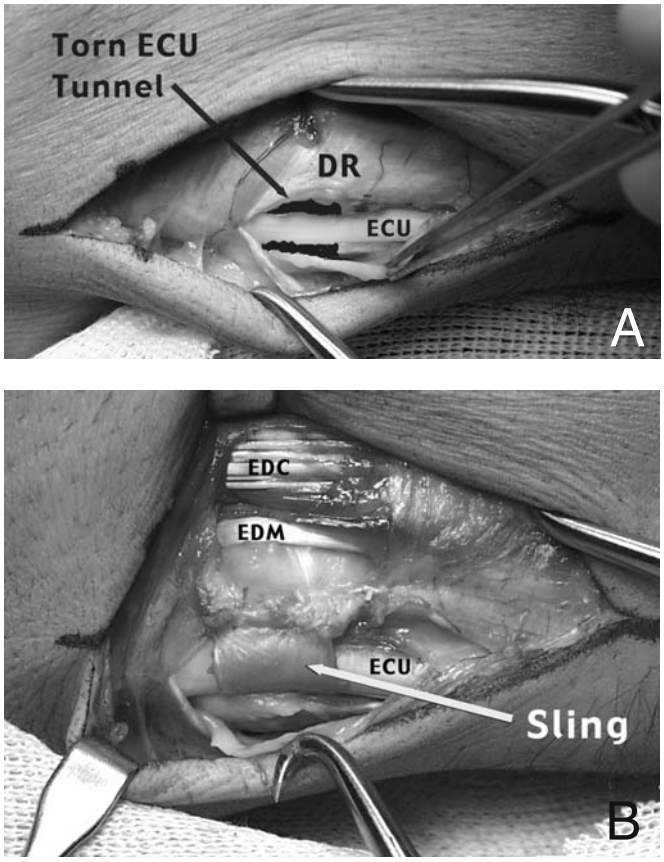

FIGURE 15-2. (A) A 33-year-old professional athlete who sustained direct trauma to the dorsum of the wrist 10 weeks before coming to our attention. He had been treated with taping, but continued to have pain on daily activities, particularly with pronosupination of the wrist. He had pain radiating from the wrist up the arm, particularly with supination, and has been diagnosed with tendinopathy. The edges of the ruptured ECU tunnel are marked in black below the dorsal retinaculum (DR). The forceps are grasping the edge of synovium that is often infolded and tacked down to the tunnel, giving the appearance of a normal tunnel. Only when this synovium is peeled back can the rupture be truly appreciated. (B) The tunnel is reconstructed. The arrow points to the sling that has been constructed from the dorsal retinaculum. The synovial side is toward the tendon to prevent tenodesis. This is accomplished by taking a band of dorsal retinaculum and bringing it under the ECU before suturing the end back to the edge of the 4–5 compartments. It is necessary to reinforce the 4–5 interval before final suturing.

2. Extensor Carpi Ulnaris Subluxation/Dislocation

ECU subluxation/dislocation usually results from an athletic trauma with a fairly well-defined mechanism of hypersupination combined with ulnar deviation and wrist flexion. This causes a volar displacement of the tendon as an acute longitudinal tear of the fibro-osseous tunnel occurs on the ulnar side. Unfortunately, this tendon disorder is rarely seen in its acute stage, the pain most commonly being attributed to a "wrist sprain." Patients will generally present many weeks or months after the injury with persisting dorsal-ulnar wrist pain and a clicking sensation, which is sometimes audible. Clinical examination reveals minimal tenderness over the sixth extensor compartment with normal range of motion (ROM). The pain and clicking sensation are reproduced with active forearm supination and wrist extension as the ECU tendon dislocates from its fibro-osseous tunnel. Performing these maneuvers passively will rarely reproduce the symptoms. Pronation of the forearm returns the tendon

to its anatomical position. If the ECU tendon is dislocatable, then the diagnosis is obvious. If not, then the differential diagnosis must include intra-articular pathology as a possible source of the clicking sensation, in particular TFCC tears. Otherwise, all dorsal-ulnar pathologies (Table 15-1) must be considered.

Provocative test: Combined forearm supination with wrist extension.

Management

When acute recognition of the condition occurs, first-line nonoperative management includes long-arm casting with the forearm in pronation and the wrist in slight radial deviation and extension for 6 weeks. This will potentially allow healing of the torn ulnar border of the fibro-osseous tunnel, preventing further displacement of the ECU tendon. While nonoperative management is suggested for management of acute ECU subluxation [46], Rowland et al. [49], in their experience with a 59-year-old physician, suggest that primary operative repair is preferable to casting. Clearly the data are limited, as recognition of acute ECU injuries is rare.

If symptoms of pain and clicking persist despite an adequate course of casting followed by rehabilitation, then surgical repair is indicated. Uniformly good results have been achieved with operative reconstruction of the fibro-osseous tunnel in chronic cases by a number of authors [46–48] using several techniques. Once again, these results are based on a limited number of case reports (11 in total for these 3 authors) but the results are encouraging. This is performed through a dorsoulnar, longitudinal incision over the sixth extensor compartment. The subluxating tendon is identified, and a longitudinal rent in the ulnar-restraining wall of the fibro-osseous tunnel is visualized. Except in an acute situation, primary repair without augmentation will rarely be successful. Most often, reconstruction using a radially based sling about the ECU tendon with a portion of the extensor retinaculum, in addition to primary repair, will be necessary (Figure 15-2) [46]. Postoperatively the arm is maintained in a long-arm cast at 90 degrees of elbow flexion, neutral forearm rotation, and 30 degrees of wrist extension for 6 weeks. If the dorsal structures are attenuated, then a portion of flexor carpi ulnaris (FCU) can be passed through a drill hole in the ulna and used to reconstruct the tunnel [46].

3. Extensor Digiti Minimi Tenosynovitis

The extensor digiti minimi (EDM) originates from the common extensor origin of the lateral epicondyle. It inserts at the proximal phalanx of the little finger and into the dorsal expansion of the finger extensor tendons after passing through the fifth extensor compartment. Schenk dissected 57 hands and found duplications of the EDM in 48 (84%) [51]. Thus, it is unlikely that duplication presents a predisposing factor as it does in de Quervain's tenosynovitis.

Patients present with pain and swelling on the ulnar-dorsal aspect of the wrist just distal to the head of the ulna. It can be seen following wrist injury but generally occurs after repetitive use of the hand, such as with handwriting activities. The patient has pain with gripping and is unable to extend the little finger. On examination, there is reproduction of the pain with attempts to flex the wrist after making a fist. The differential diagnosis includes ECU tenosynovitis/subluxation, TFCC pathology, and posttraumatic ulnar impaction.

Provocative test: Flexion of the wrist after making a fist.

Management

If the patient is not responsive to standard nonoperative therapy, surgical decompression should be performed through a longitudinal incision over the swelling of the fifth extensor compartment. The dorsal branches of the ulnar nerve must be preserved. The sheath will be thickened and is completely released.

Results

There is only one documented case report in the last 40 years where surgical decompression was performed for EDM tenosynovitis [51,52]. The patient's pain completely resolved with release of the fifth extensor compartment. There is one report of EDM tendon sheath stenosis resulting in triggering of the little finger which, upon surgical release, resulted in complete resolution of symptoms [52].

Volar-Radial Wrist Pain

1. Flexor Carpi Radialis Tendinopathy

The flexor carpi radialis (FCR) musculotendinous unit originates from the common flexor origin on the medial epicondyle and inserts via 3 distinct bands, predominantly into the base of the second metacarpal but also into the third metacarpal, with a smaller band connecting to the trapezial crest. The tendon enters a fibro-osseous tunnel at the proximal border of the trapezium, where it occupies 90% of the available space and is prone to compression [53].

FCR tendinopathy presents as pain and sometimes swelling along the radiovolar aspect of the wrist following the course of the FCR, usually at the level of the distal wrist crease. The onset of pain is generally insidious, with no history of acute trauma and frequently no identifiable source of repetitive trauma, although activities involving repetitive wrist flexion may have been performed. Movements that exacerbate the symptoms include resisted flexion and radial deviation, as well as passive wrist extension. Confirmation of diagnosis can sometimes be obtained with the use of local anesthetic injected into the area of maximum tenderness. Differential diagnosis includes osteoarthritis of the first carpometacarpal joint, scaphoid cysts, fracture, ganglia, de Quervain's tenosynovitis, and Linburg's syndrome. A lack of clinical suspicion commonly results in delayed diagnosis and treatment [54].

Provocative test: Combined wrist flexion and radial deviation resisted from a neutral wrist position.

Management

Failing nonoperative management, surgical decompression is warranted. This is performed through a volar longitudinal incision immediately radial to the FCR curving radially onto the thenar eminence. Care must be taken to protect the palmar cutaneous branch of the median nerve ulnarly and the antebrachial branch of the superficial radial nerve radially. The thenar muscle origin is raised from the transverse carpal ligament radially to expose the FCR sheath. The sheath is incised in a proximal-to-distal direction. Complete release includes mobilization from the trapezial groove, releasing the trapezial insertion. Operative findings include synovitis, adhesions, complete rupture, exostosis, stenosis, and anomalous tendon insertion. Consequently, additional procedures are frequently required at the time of initial surgery. Complete decompression is usually sufficient to relieve symptoms, and complete synovectomy is rarely indicated.

Results

A review of the English literature reveals only 5 relevant articles targeting this uncommon disorder. A retrospective study by Gabel et al. [54] reviewed the results of surgical decompression in 10 patients (mean age 44 years) who failed nonoperative treatment. At an average follow-up of 44 months, 9 of 10 patients had relief of symptoms and were able to resume their preoperative employment and leisure activities. Fitton et al. [55] obtained good results with surgical decompression in 11 of 12 patients. Long duration, workers' compensation, and failure to respond to local injections are associated with poor results.

Midvolar Wrist Pain

1. Carpal Tunnel Syndrome

Although carpal tunnel syndrome (CTS) can be related to FDP/FDS tenosynovitis [59], it is more appropriately categorized as a nerve compression syndrome and as such will not be discussed any further in this chapter.

2. Linburg's Syndrome

Linburg's syndrome involves an anomalous connection between flexor pollicis longus (FPL) and the index flexor digitorum profundus (FDP). This is a fairly common anomaly found unilaterally in 20% to 31% and bilaterally in 7% to 14% of the general populace [60,61]. The pathological form of this anomalous connection has been termed thumb-index flexor tenosynovitis [62]. In symptomatic patients, there is some controversy as to whether or not this anomalous tendinous connection is the result of tenosynovial adhesions [61] (acquired lesion) or simply a congenital anomaly that predisposes the development of thumb-index flexor tenosynovitis (congenital lesion). It was once hypothesized that carpal tunnel syndrome was associated with Linburg's syndrome [60]. This has subsequently been disproved [62].

Patients with symptomatic Linburg's syndrome (thumb-index flexor tenosynovitis) present with a several-months history of vague, poorly localized, activity-related pain on the distal aspect of the volar forearm and wrist. There may be a sensation of tightness and sometimes cramping of the thumb [43]. The patient may have noted a lack of independent flexion of the thumb and index finger prior to the development of symptoms, although this is a very subtle finding. There is usually no history of trauma, and the symptoms are of insidious onset. Physical examination reveals simultaneous flexion of the index finger with active flexion of the thumb interphalangeal (IP) joint. Passive extension of the index finger while actively flexing the IP joint of the thumb may reproduce the pain [63].

Provocative test: Passive extension of the index finger while actively flexing the IP joint of the thumb.

Management

In the absence of symptoms, the presence of the anomalous intertendinous connection, as demonstrated by the

above-mentioned provocative test, does not warrant any form of treatment. In the symptomatic individual, nonoperative therapy is rarely effective but should still be attempted, since the diagnosis may not always be clear. Steroid injections of the FPL sheath may give short-term relief but rarely provide long-term relief [62].

Operative release of the intertendinous connection between the FPL and the index FDP is relatively simply accomplished through a longitudinal incision over the FCR/radial artery interval (distal part of Henry approach) extending into the carpal tunnel. Once the FPL and index FDP are identified and the neurovascular bundle is protected, the interconnecting tendinous slip or hypertrophic tenosynovium is isolated and divided.

Results

Lombardi et al. [62] explored 26 wrists in 24 patients with volar wrist and forearm pain and a positive provocative test in whom conservative management, including steroid injection, had failed. All patients had hypertrophic tenosynovium connecting the FPL and index FDP and more than half had a tendinous slip. In 17 wrists with greater than 6 months follow-up, 76% were improved by surgical management.

Volar-Ulnar Wrist Pain

1. Flexor Carpi Ulnaris Tenosynovitis

Flexor carpi ulnaris (FCU) tenosynovitis is seen most commonly in golf and racquet sports athletes [4]. Overall, it is the most common wrist flexor tendinopathy [63]. It presents clinically with pain and swelling just distal to the pisiform, hence the difficulty in differentiating it from pisotriquetral arthritis, which is also seen in this group of athletes. Also in the differential diagnosis is Guyon's canal syndrome, which may result from localized inflammation and ulnar nerve compression or neuritis [63]. In FCU tenosynovitis, pain is reproduced with passive wrist extension as well as resisted wrist flexion combined with ulnar deviation, thus differentiating it from other pathological conditions. Twenty-degree supinated oblique lateral radiographs may occasionally aid in diagnosis by revealing calcific deposits at the FCU insertion near the pisiform [16].

Provocative test: Pain with resisted wrist flexion and ulnar deviation.

Management

Nonoperative treatment including steroid injections and dorsal splinting is generally successful. Surgical intervention may simply involve excision of calcific deposits, lysis of peritendinous adhesions [4], or, in more advanced cases, lengthening of the FCU using a 5-mm Z-plasty with excision of the pisiform [64].

Results

Despite FCU tenosynovitis being the most common wrist flexor tendinopathy, there are few published results of operative intervention in the English literature. This is probably a result of the high success rate of nonoperative intervention.

2. Trigger Finger

This is one of the few tendinopathies that manifests in the hand itself. It is most commonly idiopathic [4] but can occur from repetitive blunt trauma to the A1 pulley at the base of the fingers or thumb [43]. It is associated with other tendinopathies, bursitis, and diabetes among other disease entities. It can be associated with racquet sports due to direct pressure on the A1 pulley from a forceful grip on the racquet handle. Other sports associated with trigger finger include handball, baseball (catchers), gymnastics, weightlifting, and golf. Ultimately, inflammation of the tendon occurs, and the pathological triggering results from a disproportion between the flexor tendon and its sheath (pulley) [4].

Patients present with a complaint of snapping or triggering with flexion or extension of the involved digit, which may or may not be painful. Occasionally patients will present with a locked digit. It is usually seen in the dominant hand of a woman in her fifth or sixth decade. It most commonly affects the ring and middle fingers, and less frequently the thumb. On examination, a nodule is often palpable at the level of the metacarpal head and A1 pulley. With prolonged locking, a flexion contracture can develop at the proximal interphalangeal (PIP) joint. The differential diagnosis of triggering includes a locked metacarpophalangeal (MCP) joint, a subluxating MCP joint, a tendon tumor, or a partial tendon laceration [63].

Management and Results

Nonoperative management including corticosteroid injections into the tendon sheath and splinting in 15 degrees of flexion [67] is successful in 36% to 84% of the cases [68–76]. Up to 28% of patients will require more than one injection [75]. Lapidus reported spontaneous resolution in 29% of patients with trigger finger. Predictors of poor outcome with conservative management include systemic inflammatory conditions such as rheumatoid arthritis [71] and diabetes [65,77,78], multiple digit involvement [74], and duration of symptoms longer than several months [79,72,76].

Failing conservative management, surgical release of the A1 pulley is indicated. Pathological changes of hypertrophy in the sheath are the most remarkable feature of trigger finger. The incision can be done in an open [14] or percutaneous fashion [67,80,81] under local anesthesia [82]. We prefer the open technique, as it ensures complete release of the pulley and allows visualized protection of the digital nerve. Very little recovery time or functional improvement gain results from percutaneous release. The A1 pulley is approximately 1 cm wide extending from 1 to 2 cm proximal to the proximal digital crease. A 1.5-cm transverse incision is made at the level of the metacarpal neck. The palmar fascia and flexor tendons and sheath are exposed with blunt dissection as the digital nerves are identified and protected. The demarcation between the A1 and A2 pulley is identified. The A1 pulley is then split longitudinally along the radial border for D2, D3, and D4, and along the ulnar border for D5. The digit is then taken through ROM to ensure complete release. In the thumb, a transverse incision should be made at the level of the MP flexion crease. Particular attention should be paid for the radial digital nerve, as it lies close to the deep layer of dermis at the flexion crease and can be easily transected.

Surgical release is very successful. Complete resolution of triggering can be expected in up to 97% of patients [83]. Important complications include nerve injury, painful scars (the most common complication), stiffness, infection, bowstringing, and recurrence or incomplete release [63]. Thorpe [84] reported a 40% complication rate in a series of 43 patients. Thus, surgical release, although highly successful, is not necessarily a benign procedure. Failure of resolution may be attributable to more distal stenosing tenosynovitis. Rayan [85] reported 3 patients with stenosis of the A3 pulley that resolved with surgical release.

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16
Groin Tendon Injuries

Per Renström

Injuries to the groin, hip, and pelvic area are common in sport, occurring at the rate of 0.69 per 1000 hours of activity. Groin injuries in football have been estimated to be 5% [1], 5% [2], and 6.2% [3], with the injury rate to the adductor tendons estimated by the National Collegiate Athletic Association (NCAA) at 0.25 per 1000 hours.

The symptoms from the groin may be vague and often uncharacteristic. It is therefore important to have a broad list of differential diagnoses available. The injury can involve adductor muscle tendon problems, but other tendons may be involved. Sports hernia, a posterior inguinal wall insufficiency, is probably very common. Other causes may be osteitis pubis, neurally referred pain, hip problems, snapping hip, bursitis, tumors, intra-abdominal problems, etc.

Groin pain may have a diffuse picture and be caused by many different diagnoses. Obviously, specific diagnosis should be used, but, until a given diagnosis is verified, it is acceptable to talk about "groin pain syndrome," though some health care workers still prefer the old nomenclature of "adductor syndrome," "adductor strain," "pain secondary to unstable pelvis," "sports hernia," or "athletic pubalgia."

However, what is the true pathology? If we know this, can we offer effective management? As the so-called sports hernia is an insufficiency of the posterior abdominal wall, we should probably not use the term "hernia," and indeed "athletic pubalgia" may be a better expression.

Tendon Injury Problems in the Groin Area

Without a stable and well-controlled pelvis, it is hard to perform with skill in sports such as tennis, hockey, soccer, squash, rugby, Australian rules football, etc. The pelvis connects the upper and the lower body. Multiple muscles and tendons insert into the pelvis, and a delicate balance exists between these structures to coordinate the movements passing through the pelvis. The hip joints connect the lower limbs with the pelvis. There is a biomechanical balance between the adductors and the abdominals. There is some "give" around the pubic symphysis. The motions involved are about 2 mm in longitudinal shear, and 3 mm in rotation. The cause of a groin problem may be a combination of abdominal hyperextension and thigh hyperabduction with the pivot point at the pubic symphysis [4]. The repetitive contractions of strong adductors may affect this complex, and weaken the posterior abdominal wall.

Muscle tears tend to occur at the musculotendinous junction, a complex area that contains Golgi organs and nerve receptors. The musculotendinous junction contains cells that can elongate rapidly and deposit collagen, and the tendon elongates when this occurs. Variations in the extent of the interdigitations of the tendon into the muscle at the origin and insertion may explain the site of tears.

Injuries to the adductor muscle–tendon unit occur at the insertion of a tendon into bone, the osteotendinous junction. There are many muscles associated with the groin such as the quadriceps muscles being both knee extensors and a hip flexor (the rectus femoris). The sartorius muscle is a hip flexor and rotator, as well as a knee flexor and rotator. The hamstring muscles (biceps femoris, semitendinosus and semimembranosus) are both hip flexors and knee rotators. The adductors (adductor magnus, adductor longus, adductor brevis, gracilis, and pectineus) are hip adductors, hip flexors, and hip rotators. There are variations in the shape and extent of the adductor longus tendon. (See Chapter 1.) Depending on the position of the hip, the posterior part of the adductor magnus can work as an extensor the hip joint. The gracilis can also flex and medially rotate the knee joint. The abductors and gluteal muscles (tensor fascia lata, gluteus maximus, medius, and minimis) are hip abductors,

hip extensors, medial and lateral hip rotators, and hip flexors.

The piriformis, gemelli, obtoratorius externus and internus, and quadratus femoris are both lateral hip rotators and hip abductors when the hip is flexed. The iliopsoas muscle is primarily a hip flexor but also a lateral hip rotator and a flexor of the lumbar spine. All the above muscles are also active as stabilizers of the hip joints and the pelvis, and thereby the trunk. This is especially evident when they work eccentrically. Using this approach, the importance of the adductors as a major muscle group, and not only "adductors" of the femur in the nonweightbearing situation, becomes evident.

Diagnosis

History and Symptoms

The diagnosis is often made from the history. The "common groin pain" history reported by an athlete can precisely pinpoint the time of onset of pain. The problems often arise during preseason training, and are much more common in males. Patients often report pain during the activity, localized to the pubic region, but often radiating proximally and distally, and often bilateral. Especially in chronic cases, it may mimic nerve entrapment and spinal conditions, and problems in the abdominal organs and sacroiliac joints.

When the pain is *adductor-related*, it is more medial in the groin, and may radiate along the adductor muscle group. When the injury is *iliopsoas-related*, the pain is localized more anteriorly in the proximal thigh, more laterally in the groin. It sometime radiates along the anterior aspect of the femur, and at times involves the lower abdomen lateral to the rectus abdominis. Myotendinous pain in the *lower abdomen* is most prominent around the conjoint tendon insertion on the pubis, and may radiate into the adductor region and the testes [5]. Chronic injuries related to the *rectus femoris* or the *sartorius* are less common. They are usually located at the proximal end of the muscle and tendon close to the insertion.

Examination

Physical examination will often support the suspected diagnosis. There is often pain on resisted adductor motion, and typically there is progression towards chronicity. Physical examination should be focused on the region indicated by the history. An assessment of the patient's gait and posture is useful. The region should be inspected for swelling, discoloration, and other abnormalities. The range of motion of the hip joints, lumbar spine, and the knee joints should be assessed. Various functional tests to evaluate balance and pelvic stability can be performed, including one-leg balance test, exercises on a soft surface, and lunging. Physical examination should include systematic palpation and functional testing of the muscles and ligaments based on the anatomy and biomechanics, with evaluation of flexibility of the lumbar spine and the knee.

Diagnostic Aids

- Plain radiographs are usually the first choice in most conditions involving the pelvis and the hip joints.
- Tomography and computed tomography (CT) are an important supplement in the case of fractures and can be very helpful in preoperative planning.
- A technetium-99 m triple-phase bone scan can be helpful, as increased uptake can be seen in stress fractures, bone neoplasms, bone infections, and osteoarthrosis. In patients with enthesopathy of the adductors and rectus femoris insertion, a bone scan will often show increased uptake.
- Magnetic resonance imaging (MRI) has obvious advantages, including the lack of ionizing radiation, high sensitivity, capability to show soft tissue, and multiplanar imaging capability. T2 weighted images can evidence muscular and musculotendinous injuries as high signals showing muscle strains, inflammation, or ruptures.
- Ultrasound is another possibility in many patients with soft tissue problems in the pelvic region, as it is cheap, fast, and offers the opportunity of dynamic real-time scanning.

Adductor Muscle Tendon Injury

Adductor strain, especially of the adductor longus, is common in soccer [1]. The mechanism is most commonly eccentric adductor muscle contraction with concomitant hip external rotation-adduction. Fatigue, overuse or acute overload of the adductor muscles during sports activities can lead to injuries. The adductor muscles act as stabilizers of the hip joint, and are therefore at risk if the load on the hip joints and the pelvis is no longer balanced. Injuries influencing the stability of the hip joints and the pelvis might thus precipitate overuse problems of the adductor muscles.

Diagnosis

- Diagnosis is made from the history. The typical complaints are pain and stiffness in the groin in the morning and at the beginning of athletic activity. Pain and stiffness decrease, and sometimes disappear after warm-up, but may reappear when the athlete gets tired or after sport has ceased.
- The athlete usually can run in straight lines and at a moderate speed with no pain, but with increasing speed

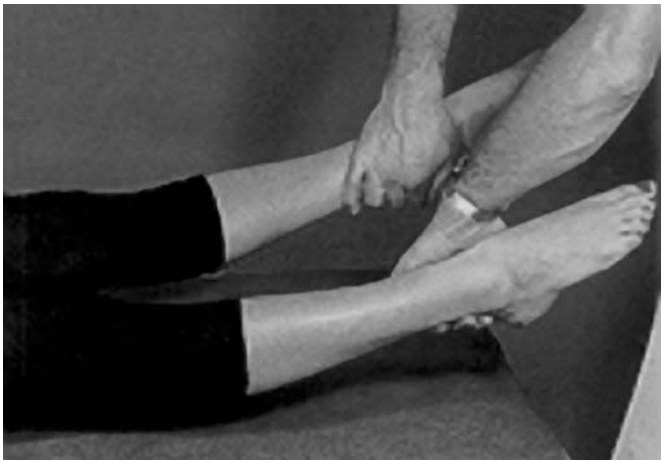

FIGURE 16-1. Resisted adduction may cause discomfort. (See color insert.)

and sudden changes of direction, groin pain ensues. Activities causing pain typically include sprinting, cutting movements, kicking the ball, and sliding tackles.
- The diagnosis verified by the resisted adductor stress test, performed with the athlete supine with the hips abducted (Figure 16-1), with pain localized to the groin. Groin pain on full passive abduction, often with a decreased range of abduction, is also frequent.
- The diagnosis suggested by the localized tenderness (Figure 16-2) at the origin of the adductor longus and/or the gracilis on the inferior pubic ramus. Tenderness over the pubic symphysis and sometimes at the insertion of the rectus abdominis on the pubis are often seen with adductor-related groin pain.

Management

- Active rest, namely carrying out activities that do not cause pain. Painful activities should be avoided.
- Early passive range of motion exercises and the use of crutches after the first few days.
- Strengthening of the abdominal, hip adductor, and hip flexor muscles is important, with unresisted isometric contractions progressing to resisted isometric exercises. Eventually, dynamic exercises may be started within the patient's threshold of pain.
- Restoring muscle strength and balance around the pelvis is extremely important to avoid relapse or development of chronic injury when the adductors are involved,
- Proprioceptive exercises to restore pelvic balance and coordination should be combined with a careful stretching program.
- Functional activities can then start, with closed chain exercises and crossover activities.
- A water training program can be helpful.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) can sometimes be tried during the first 2 to 7 days.
- Deep massage may be beneficial.
- Sport-specific exercises can be initiated when the initial exercise program can be performed without pain and the muscle coordination is adequate, before a gradual return to sport. It may take 4 to 8 weeks, or even longer, before attempting to return to sport-specific training, depending on the extent of injury.

How effective is the exercise program for this chronic injury? A prospective, randomized clinical trial found that a specific exercise program to be highly effective in the management of adductor-related groin pain [6]. The trial included 68 male athletes, with 75% of the patients training more than 3 times a week, and an average injury duration of 9 months, with 75% of them having ceased to participate in sport. One group received physiotherapy without specific training. The second group received a training program including static and dynamic exercises aimed at improving the muscles stabilizing the pelvis and the hip joints, in particular the adductor muscles. Both groups received the same amount of physiotherapy, and after the treatment period they received identical instructions about sport-related rehabilitation before returning to sports participation. At follow-up 4 months after end of treatment, 79% of the patients in the exercise group versus 14% in the physiotherapy group were without pain at clinical examination and could participate in sport at the same or a higher level of activity before the injury, without groin pain. The patients' subjective assessment was in accordance with the objective outcome measures. Hence, an active training program can improve strength

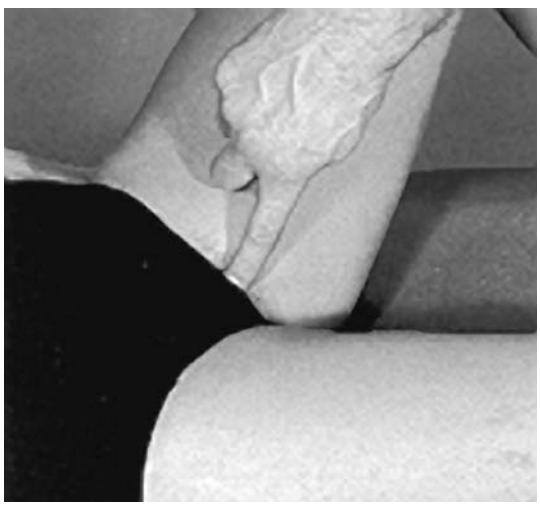

FIGURE 16-2. Localized tenderness at the adductor insertion may support the diagnosis. (See color insert.)

and coordination and relieve pain. Most patients can be managed successfully with the abovementioned training program combined with management of concomitant injuries.

- A steroid injection may occasionally be of value.
- Surgery is the last resort. The most common surgical procedure is tenotomy of the adductor longus, which is indicated only in truly chronic cases with longstanding problems. The procedure usually produces around 80% good results [7]. The adductor longus tendon should be released 2 to 3 cm distal to its attachment on the pubis, and multiple longitudinal tenotomies should be performed in the osteotendinous area [4]. Others suggest a tenotomy of the gracilis tendon close to its attachment combined with a rectus abdominis plasty or a tenotomy of both the adductor brevis and the gracilis combined with lengthening of the adductor longus.

Other Muscle Tendon Injuries

The iliopsoas muscle contributes to pelvic stability, and is involved constantly in most sports activities. The precise functions of the iliopsoas muscle are not yet fully understood, but the muscle works as pelvic stabilizer as well as a stabilizer for the lumbar spine. One reason why the muscle is at risk could be that its workload includes both eccentric and concentric work. When the injury is iliopsoas-related, the pain is localized anterior of the proximal thigh, more laterally in the groin, may radiate to the anterior aspect of the femur, and sometimes produce some lower abdominal pain lateral to the rectus abdominis. Iliopsoas-related groin pain is:

- Produced when palpating the muscle through the lower abdomen combined with pain at passive stretching of the muscle using the Thomas test [5].
- Frequently, the muscle is also tight, and palpation just distal to the inguinal ligament is often painful. Palpation is performed above the inguinal ligament and lateral to the rectus abdominis. The iliopsoas can also be palpated in the area just below the inguinal ligament lateral to the femoral artery and medial to the sartorius muscle, the only area where the iliopsoas is directly palpable. The Thomas test should be performed to assess the tightness of the iliopsoas, and to ascertain whether passive stretching is painful.
- Incomplete extension of the hip when performing the Thomas test is a sign of a tight iliopsoas muscle. Pressure by the examiner's hand to extend the hip further is a test for pain on passive stretching. The abovementioned tests for the iliopsoas were all found to be reproducible.
- Muscle weakness and pain when flexing the hip joint against resistance at 90° is often found. Sitting with the legs stretched and then elevating the heels might result in pain since the only active hip flexor in this position is the iliopsoas. This is the Ludloff's sign.

Management includes stretching and both concentric and eccentric strengthening combined with pelvic stabilization and balance exercises. Supplementary physiotherapy, including massage and trigger point stimulation, might also be helpful. If the treatment is not progressing satisfactorily, a steroid injection can be helpful. The injection can be ultrasound guided. If ultrasound is not available, the injection can be made in the area under the inguinal ligament, lateral to the femoral vessels and nerve, and medial to the sartorius muscle.

Myotendinous Pain Localized to the Lower Abdomen

This pain syndrome is most prominent around the conjoint tendon insertion at the pubic bone and may radiate into the adductor region and to the testes. Muscle-tendon injury may occur in this region but the most common cause is "sports hernia."

"Sports hernia"

This injury has become a common diagnosis, and encompasses terms such as "sports hernia," "sportsman's hernia," "incipient hernia," "Gilmore's groin," "pubic pain," and "athletic pubalgia." The lesions seem to be nonspecific and difficult to describe precisely. The pathologic findings at surgery are described as "thinning of the fascia," "loose-feeling inguinal floor," "tendency to bulge," or "weakening of the transversalis fascia."

The diagnosis is supported by:

- History, which may include an often insidious onset and deep seated pain which may radiate. There is testicular pain in 30% of patients. Kicking a ball may cause sharp pain.
- In 40% of patients, physical examination may reveal tenderness located in the adductor region. Patients may also show tenderness in the inguinal canal, especially at the posterior wall. Cough impulses may cause discomfort.
- Herniography may verify the diagnosis, which includes contrast leaking intra-abdominally. A hernia can be found with herniography in 25% of athletes with longstanding, unclear groin pain [8].
- Lesions of the symphysis may be the result of strain of tendons, ligaments and fascias. This may predispose for an inguinal hernia as well.
- Gwanmesia et al. [9] examined 32 herniograms: Of these, 25 well identified groin hernias. Twenty-one patients had surgery, and 19 hernias were confirmed. Sixteen patients had no hernia. Herniography is con-

sidered a safe and reliable technique for occult groin hernia.
- MRI depicted well the anatomy [10] in a study of 20 patients, 11 of whom had occult hernias at herniography. MRI revealed 8 occult hernias, and identified 3 cases of osteitis pubis. Hence, herniography is the primary tool for diagnosing hernias. If no herniae are found, MRI scanning may be indicated.

Management

- Nonoperative management is rarely successful in patients with a true sports hernia, but not all hernias are symptomatic. Therefore, diagnosis can be difficult. It is always wise to initially treat groin pain conservatively, avoiding painful activities for some weeks with gradual return to activities thereafter. If the pain continues despite these measures and no other problem is detected, sports hernia is the likely cause.
- Surgery can be effective. Gilmore's groin is a groin disruption with torn external oblique aponeurosis, torn conjoint tendon, conjoint tendon torn from the pubic tubercle, dehiscence between conjoined tendon and inguinal ligament, and no actual hernia present [2]. Most of his patients (98%) were males. Management of painful sports hernia is through operative repair of the weak posterior inguinal wall. A variety of open surgical procedures have been described to reinforce the posterior wall, either by plication and tightening of the existing tissue or by reinforcement with mesh. Recently, laparoscopic procedures have been developed, with placement of a synthetic mesh over the defect superficial to the peritoneum.

Results

The diagnosis of sports hernia may be difficult, and requires an experienced clinician. Early surgical intervention is usually successful, and 85% to 90% of patients return to full activity within 2 to 3 months [11,12]. A successful return to sports following an open procedure is possible in about 90% of athletes. Brannigan et al. [13] followed 100 consecutive groin repairs in 85 young athletes treated with Gilmore's repair: 96% of them returned to competitive sports in 15 weeks. Recent preliminary reports suggest that laparoscopic surgery with implantations of a polypropylene mesh may allow return to full sports activity in <1 month.

The "hockey groin syndrome," with tearing of the external oblique aponeurosis and entrapment of the ilioinguinal nerve, is a cause of groin pain in professional hockey players. Ilioinguinal nerve ablation and reinforcement of the external oblique aponeurosis successfully treats this incapacitating entity. In a 12-year study, 22 NHL ice hockey players with debilitating groin pain underwent surgery with exploration of the inguinal nerve and reinforcement of the external oblique aponeurosis with a Gore-Tex graft. Subsequently, 85% were able to continue their careers in ice hockey [14].

Meyers et al. [4] evaluated 276 patients. Of these, 138 had adductor pain and 38 had other abnormalities. One hundred seventy-five pelvic floor repairs were carried out. Of the 157 patients who had received a rectus abdominis muscle reattachment, 97% returned to their earlier levels of performance. A distinct syndrome of lower abdominal/adductor pain in athletes, "athlete's pubalgia," is correctable by strengthening the anterior pelvic floor.

Osteitis Pubis

This entity was first described by Beer in 1924 as causing groin pain in activities such as kicking a football. Osteitis pubis presents with pain at the pubic symphysis that can be referred to the surrounding area to include the lower abdomen, hip, groin, scrotum, or perineum. Its etiology is unknown. However, abnormal biomechanics of the pubic symphysis has been implicated as the probable cause. Pubic symphysis motion in normal subjects is restricted to less than 2 mm. In one radiographic study, all patients with more than 3 mm of mobility had pubic symphysis pain. It is probable that stiffness and restricted motion of the hips and sacroiliac joints contribute to increased motion and stress being placed on the pubic symphysis.

The diagnosis is made by plain radiography, and can be assisted by technetium-99m isotope bone scanning, which will show increased uptake at the pubic symphysis on the delayed views, indicating increased bone turnover. However, Fricker et al. [15] reported poor correlation between radiographic changes and clinical symptoms, with some symptomatic patients having no radiographic changes or isotope uptake on bone scan. In addition, radiographic changes and bone scan isotope uptake did not correlate well with the duration or intensity of symptoms. MRI will normally clarify the diagnosis.

Management

The initial management consists of a program of varied exercises. Therapies which may help to speed recovery up have been advocated, but have not been scientifically validated. The first line of management is reduction of activity levels. Cyclic activities such as running should be substituted with non-painful activities such as swimming, and appropriate stretching and strengthening exercises of the surrounding joints and musculature should be instituted. Particular attention should be paid to hip range of motion, and adductor stretching and strengthening. Shock-absorbing footwear may also play an important role in reducing the shear forces across the symphysis. Corticosteroid injection under fluoroscopic guidance

may be effective. The management is basically conservative, as the condition is mostly self-limiting. Full recovery for men occurs on average in 9 months, and in women in 7.5 months [15].

Groin Pain of Neural Origin

Peripheral nerves may become entrapped after direct trauma or inflammation. The nerves most commonly affected are the ilioinguinal, genitofemoral, and lateral cutaneous femoral nerves. The femoral, obturator, and iliohypogastric nerves may also be involved, though rarely.

In a study of 27 cadavers, the course of genital branches around the inguinal region varied considerably [16], and entrapment of any of these branches by the inguinal ligament might cause groin pain. Neural factors may play a role in groin pain produced by groin hernia.

Lee and Dellen [17] studied 54 patients with groin pain related to resection of lateral femoral cutaneous, ileoinguinal, iliohypogastricus, or genitofemoral nerves. Resection of the ileoinguinal and iliohypogastric nerves gave 78% to 83% excellent results. The worst result was achieved with resection of the genitofemoral nerve, with only 50% of patients gaining excellent outcome.

Intra-Articular Hip Problems

A not uncommon hip problem in athletes is labral tears of the hip joint, which often cause a sharp catching pain. Flexion and rotation of the hip usually initiate pain. An intra-articular injection of local anesthetic can be diagnostic. MR arthrogram can be recommended given its accuracy of 91% in identifying a labrum tear. The labrum tear can be managed arthroscopically with excision of the tear or, more commonly, excision of the labrum. Mitchell et al [18], in a prospective study of 25 consecutive hip arthroscopies, found that all of the hips arthroscoped had pathology. Back pain and hip pain were the most common presentations. The only consistently positive clinical test result was a restricted and painful hip compared with the contralateral hip. Of the 17 patients whose flexion, abduction, and external rotation results were reported at the time of examination, 15 (88%) were positive, and 2 (12%) were negative. Plain radiographs were normal in all patients. All but one patient underwent magnetic resonance arthrography. Although specificity of 100% was achieved in that study, the sensitivity was significantly lower, with a relatively high number of false negatives.

Narvani et al. [19] studied the prevalence of acetabular labrum tears in athletes presenting with groin pain. Eighteen athletes who presented to their sports clinic with groin pain underwent clinical assessment and MR arthrography to detect presence or absence of acetabular labrum tears. In 4 of these 18 athletes (22%), the MR arthrogram demonstrated the presence of acetabular labrum tear. Three of them underwent arthroscopic debridement of their acetabular labrum tears and returned to their sporting activities within 8 months. Clicking sensation of the hip was a sensitive (100%) and specific (85%) clinical symptom to predict labral tears. The internal rotation–flexion–axial compression maneuver was sensitive (75%) but not specific (43%). The Thomas test was neither sensitive nor specific.

Other painful intra-articular hip lesions include localized chondral lesions, chondral delamination, and chondral or osteochondral loose bodies. Their optimal management is by hip arthroscopy and debridement. If there is no serious articular cartilage injury, it may be possible to return to sport within 1 to 4 months.

Snapping Hip and Other Related Conditions

Snapping around the hip, either medially or laterally, can be ascribed to a variety of causes. It was first described by Binnie in 1913 and the internal snapping hip by Schaberg et al. [20]. The snapping sensation is audible, and is sometimes associated with pain. When no discomfort or pain is felt with the snapping, the condition is considered of no pathological significance.

One cause of medial snapping hip is impingement of the iliopsoas tendon when it is catching on the pelvic brim, or ileopectineal eminence. Other causes of medial snapping hip can include intra-articular problems in the hip or a snapping iliopsoas tendon. Intra-articular loose bodies caused by trauma, osteochondritis dissecans, or osteochondromatosis can be associated with locking, clicking, and pain. A labral tear may also result in a painful medial snapping hip. The iliopsoas tendon lies in a groove between the iliopectineal eminence and the anterior inferior iliac spine. It crosses over the femoral head and capsule and inserts into the lesser trochanter. When the hip is extended from the flexed and externally rotated position, an audible and sometimes painful snap is felt. Palpation over the hip joint can often reveal a snapping sensation against the fingers.

The snapping iliopsoas can in most cases be treated nonsurgically. A combination of stretching and careful dynamic strengthening exercises can often help the patient. Sometimes a steroid injection is needed. Surgery gives acceptable results by either lengthening the tendon or a tenotomy.

Stress Fractures

Many stress fractures probably go unrecognized because the patients treat themselves by resting until the pain improves. Stress fractures of the pubic rami are particlurly common among long-distance running athletes.

There appears to be an association with anorexia and amenorrhea among female athletes. Stress fractures have been reported to occur in 49% of collegiate female distance runners who had <5 menses per year [21]. In addition, of those athletes who were amenorrheic, 47% had an eating disorder.

Stress fractures present insidiously with lower pelvic and groin pain worsened with pounding type activities. The pain is often worse just after running, but will gradually improve with rest. Stress fractures are often related to a sudden increase in the intensity of the athlete's training. Stress fractures are often not evident on plain radiographs because of the lack of callous formation. Therefore, if a stress fracture is suspected, a bone scan or MRI is the investigation of choice.

Stress fractures have been reported in all bones of the pelvis, but the most common area of pelvic involvement is the inferior pubic rami. Stress fractures of the femoral neck are the most serious concern around the pelvis. An unrecognized stress fracture of the femoral neck can go on to complete fracture with the potential for avascular necrosis. This is a potentially devastating problem, so early recognition and management is the key. One study reported on 23 athletes with femoral neck stress fractures [22]. Of the 7 patients that developed complications, 5 had a displaced fracture. This stresses the importance of early recognition and management of these injuries to prevent displacement.

Management of stress fractures about the pelvis, except for femoral neck fractures, is relatively straightforward. This involves a period of 4 to 6 weeks rest from the inciting activities. When the athlete is pain free, a graduated program of return to activities can begin. Any dietary or hormonal issues must be addressed to assist in healing and prevention of recurrence. Management of femoral neck stress fractures is based on the displacement and location of the fracture. All displaced fractures require surgery to anatomically reduce the fracture and fix it with cannulated screws. Nondisplaced fractures can be divided into 2 categories: 1) compression fractures and 2) tension fractures. The compression fractures have a good potential to heal, and can be treated nonoperatively. Activities should be restricted by pain. This usually requires a short period of nonweightbearing to partial weightbearing with crutches to prevent a complete fracture. This is followed by a gradual return to normal pain free activities. No pain should occur either during or after the activity. Progression of healing should be monitored with serial radiographs. Return to light running can usually begin at about 2 to 3 months if there is no pain and the radiographs show healing of the fracture. Tension fractures are best managed surgically using cannulated screws. Tension fractures have poor healing capacity and are more likely to progress to complete fractures. If this occurs, avascular necrosis may develop with devastating consequences. Patients with nondisplaced fractures managed surgically can return to pain-free light running at about 3 months from the procedure.

Conclusions

Many groin problems in athletes are secondary to acute injuries that have not been managed appropriately. Others are caused by muscle imbalances and poor biomechanics and, without proper rehabilitation, have resulted in chronic conditions. In most patients with longstanding problems, a hernia must be excluded.

Athletes should be aware that, if they experience groin pain, they should abstain from the activity causing symptoms until a diagnosis is formulated. If these injuries are mismanaged or, more commonly, ignored, chronic pain will result. If there is any doubt about the diagnosis, these athletes should be referred to a physician with a special interest in these problems. These physicians have often developed a multidisciplinary approach to groin injuries.

In summary, groin injuries involving tendons may not in themselves be serious. However, they may lead to chronic pain and impair athletic ability and performance, especially if not correctly diagnosed and promptly treated. Groin injuries and pain may prevent athletes from participating in sport for long periods. They still constitute some of the greatest problems in orthopedic sports medicine.

Take-Home Message

- Allow rest initially until a diagnosis is made.
- Be aware of various differential diagnoses.
- Teamwork is often beneficial.
- Management must be based on a definite diagnosis.
- Recovery and healing may take time.
- Groin pain can be very difficult for both the patient and the doctor.
- Show respect and patience for groin pain problems.
- Groin injuries may not in themselves be serious injuries. However, they may lead to chronic pain and impair athletic ability and performance, especially if not correctly diagnosed and promptly managed.

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17
Knee and Thigh Overuse Tendinopathy

Barry P. Boden

As the participation in athletic activities increases around the world, so does the frequency of tendinopathies.

- The etiology of most tendon injuries is related to repetitive mechanical overload with the development of degenerative intratendinous lesions.
- Nonoperative management consisting of activity restriction, nonsteroidal anti-inflammatory medications, correction of external factors such as overtraining, and physical therapy is successful in the majority of acute tendinosis injuries.
- Surgery is necessary for most complete tendon ruptures, and may be considered for partial ruptures and in chronic tendinopathy patients who fail a 3 to 6 month course of non-operative management.

Quadriceps Tendon

Anatomy

The quadriceps tendon connects the four extensor muscles of the anterior thigh, the rectus femoris, the vastus intermedius, the vastus medialis, and the vastus lateralis to the patella. The tendon inserts on the proximal pole of the patella and continues distally as a tendinous expansion over the anterior patella to merge with the patella tendon. Most of the fibers anterior to the patella are a continuation of the rectus femoris tendon [1].

The rectus femoris and vastus intermedius lie centrally and parallel to the femur with the rectus femoris being the more superficial muscle. The vastus medialis consists of two muscle groups based on their orientation to the patella. The vastus medialis obliquus fibers are oriented obliquely and attach more distally to the patella than the vastus medialis longus [1]. The vastus lateralis muscle fibers insert on the superolateral patella more proximally than the vastus medialis [1]. The tendinous fibers of the vastus intermedius insert directly into the superior border of the patella just deep to the remaining three tendons. While the vastus intermedius courses parallel to the femur, the line of action in reference to the femur is 15 to 18 degrees for the vastus medialis longus, 55 to 70 degrees for the vastus medialis obliquus, and 20 to 45 degrees for the vastus lateralis [3].

Imaging techniques for evaluating the quadriceps tendon include radiography, ultrasonography, and MR imaging. MRI of normal quadriceps tendons reveals a laminated appearance with 3 (56%), 2 (30%), or 4 (6%) layers [4].

Quadriceps Tendinopathy

Quadriceps tendinopathy is much less frequent than patellar tendinopathy in athletes. This may be related to the superior strength, mechanical advantage, or vascularity of the quadriceps tendon. In adolescent athletes, avulsion injuries of the proximal patellar apophysis are more common than tendinopathy of the quadriceps mechanism [5]. Patients with quadriceps tendinopathy complain of pain at the proximal pole of the patella. The pain is typically insidious, and often associated with a recent increase in jumping, climbing, kicking, or running.

Physical examination reveals tenderness over the superior pole of the patella and discomfort with resistance to extension with the knee hyperflexed. Patients should be evaluated for any malalignment entities, although no definite scientific evidence exists on a cause-and-effect relationship between factors such as femoral anteversion, increased Q angle, and tibial torsion and quadriceps tendinopathy. Quadriceps strength and hamstring flexibility should also be assessed. In young athletes with quadriceps strains, plain radiographs are usually normal. However, in older individuals with quadriceps tendinopathy, degenerative changes such as calcification in the tendon, or spur formation at the superior pole of the patella may be present. When extension strength is maintained, an MRI is rarely necessary but may demonstrate

degenerative changes at the insertion of the tendon (see Figure 17-1).

Nonoperative management is successful in the vast majority of patients with quadriceps tendinosis. This consists of activity modification, anti-inflammatory medications, and physical therapy. Once the pain subsides, therapy should concentrate on quadriceps strengthening exercises and increasing hamstring flexibility. Strengthening exercises should focus on eccentric training of the muscle-tendon complex [6,7]. The proposed advantages of eccentric exercises are based on 3 principles:

1. Length: By increasing the resting length of the muscle-tendon unit, the strain within the complex is reduced.
2. Load: Progressively increasing the load to the myotendon unit results in increased tensile strength.
3. Speed of contraction: Increasing the speed of contraction also enhances the force capacity of the muscle tendon complex [6]. Maximum eccentric contractions can generate 20% to 30% higher forces than isometric or concentric contraction [8]. Therefore, the tendon is placed in an anabolic state instead of a catabolic state, which is induced by immobilization or corticosteroid injections.

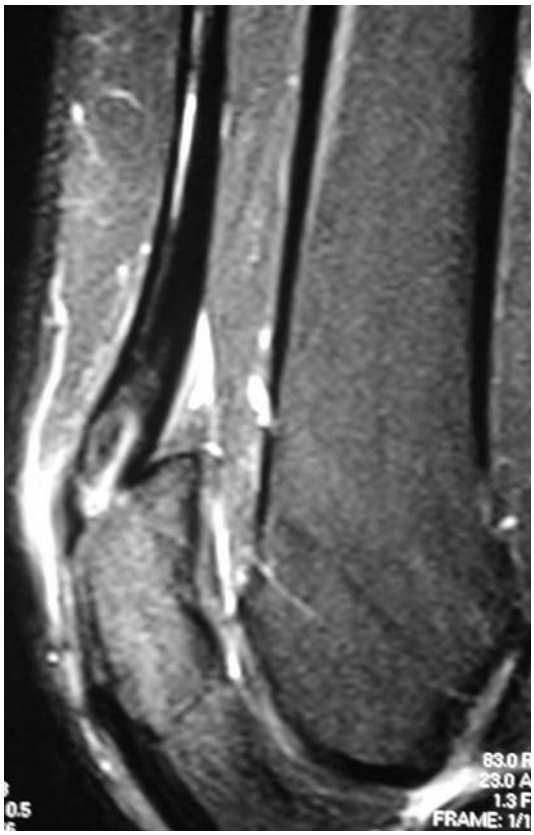

FIGURE 17-1. MRI scan of a patient with quadriceps tendinopathy. (Courtesy of Wayne B. Leadbetter.)

Eccentric training aims to strengthen the tendon so that it can withstand higher stresses. The program involves static stretching both before and after the exercises. Eccentric exercises are performed in 3 sets of 10 repetitions. With time, the speed of contractions is increased. Each week the weight applied is increased and the cycle is repeated. Most cases resolve by 2 to 3 weeks. Only rarely is surgical intervention necessary. Indications include extensive tendinopathy in symptomatic patients who have failed a 3- to 6-month trial of nonoperative management. Surgical principles include debridement of degenerative, diseased tissue, and promotion of healing by stimulating a vascular response either by longitudinal tenotomy and/or needling.

Partial Tendon Ruptures

Partial ruptures of the quadriceps tendon are rare, and require a high index of suspicion and a thorough examination for diagnosis [9,10]. Patients present with pain in the region of the quadriceps tendon, and weakness of knee extension. Often a history of a preexisting quadriceps injury can be elicited, followed by a traumatic knee injury during athletic activity. Typically, the patient is able to participate in sports with a dramatic drop in performance. If the vastus intermedius tendon is detached, which is often the case, there may be no deformity on examination. The key finding on physical examination is weakness of extension. The ability to extend the knee from a flexed position does not exclude a partial quadriceps rupture: Extension strength from a flexed position needs to be compared with the contralateral side. Although strength measurement tests may be helpful in documenting the extension deficit, there is a risk of completing the tear with maximum resistance. Plain films are usually normal, but may demonstrate degenerative calcific changes within the tendon. MRI is the best diagnostic test for identifying the location and extent of the injury.

There is a paucity of literature on the management of partial quadriceps tendon ruptures. For tears involving greater than 50% of the quadriceps tendon or tears diagnosed late, the author prefers surgical repair. When the diagnosis is made acutely, the tear involves less than 50% of the tendon, and there is no tendon retraction, nonoperative management with 6 to 8 weeks of brace immobilization may be considered. As healing progresses, the amount of knee flexion allowed by the brace may be increased. The author has seen this injury only as a tertiary referral, when the injury was chronic and the tendon retracted. In these cases, surgical repair of the partially torn tendon is recommended. Surgical repair involves a longitudinal incision over the quadriceps tendon. The rectus femoris tendon is split, without being detached, to gain access to the vastus intermedius tendon. A Krackow

stitch using nonabsorbable sutures is passed through the vastus intermedius tendon and any detached tendons. The attachment site on the anterior half of the superior patella is abraded to bleeding bone using a curette and/or bur. The tendon is then sutured to the patella through drill holes or with bone anchors.

Complete Tendon Rupture

Healthy tendons do not rupture [11,12], and preexisting degenerative changes or systemic illness must be present. Degenerative changes occur as a result of prior low-grade microtears from activity. As the tendon heals from mild insults, it develops degenerative, not inflammatory, lesions. Histologic analysis of surgical specimens reveals a disorganized matrix, increased fibroblasts and vascularity, and occasionally fatty, mucoid, or hyaline features [13]. These changes presumably weaken the tendon and predispose it to rupture. Systemic diseases, such as lupus erythematosus, diabetes, gout, hyperparathyroidism, and chronic renal failure may also weaken the tendon, making susceptible to rupture [14,15].

In general, quadriceps tendon ruptures occur in older patients than patellar tendon ruptures. The quadriceps tendon usually ruptures transversely adjacent to the osteotendinous junction. Patients report a sudden, painful pop when the extensor mechanism detaches from the patella. The rupture may occur during strenuous sports activities, squatting while lifting weights, during a fall, or after more trivial activity such as descending stairs. Complete ruptures result in immediate disability with difficulty walking.

On examination, a palpable defect in the tendon is present superior to the patella. In the acute phase, a hemarthrosis and extensive bruising can be seen. If the tear does not extend into the retinaculum, the patient may be able to partially extend the knee. However, marked extension weakness from a flexed knee position is the hallmark physical finding. The patient may manage to walk with a stiff knee and compensatory hip flexion during the swing-through phase of gait.

Plain radiographs reveal patella baja, which may be noticeable only when compared with the normal contralateral extremity. Although usually not necessary, MR imaging can confirm the diagnosis when in doubt. A disrupted tendon is best visualized on the sagittal view and is characterized by loss of continuity of the tendon and edema in the surrounding tissues (see Figure 17-2). MRI is particularly helpful in distinguishing partial versus complete quadriceps tendon injuries.

Optimal results can be achieved for a complete tear with early surgical repair. A midline incision is used to expose the quadriceps tendon and the patella. The tendon edges are debrided, and 2 Krackow stitches, using heavy nonabsorbable sutures, are placed through the entire triaminar tendon complex. The anterior half of the superior pole of the patella is debrided and abraded down to bleeding bone to stimulate healing. The tendon is then reattached to the patella through drill holes or bone anchors. Any rents in the extensor retinaculum should be repaired.

In chronic cases, when the tendon has significantly shortened or the tissue is tenuous, several techniques are available to strengthen the repair. If the tendon can be apposed to the bone but the tissue is weak, the repair may be reinforced by a flap or turndown of healthy proximal quadriceps tendon or augmented with a semitendinosus tendon [16]. If the quadriceps has shortened and cannot be apposed to the patella, a lengthening procedure with augmentation is required. Codivilla described a lengthening procedure in which an inverted V is cut through the full thickness of the quadriceps tendon 1.3 cm proximal to the rupture [17]. The triangular flap is split into an anterior part of one-third thickness and a posterior portion of two-thirds thickness. The anterior part is turned distally and the upper portion of the V is closed with interrupted suture.

The postoperative regimen depends on the security of the repair, which should be gently tested at the end of the surgical procedure. For acute repairs in healthy individuals, a long leg hinged brace is immediately applied with the range of motion set from 0 to 20 degrees. Straight leg

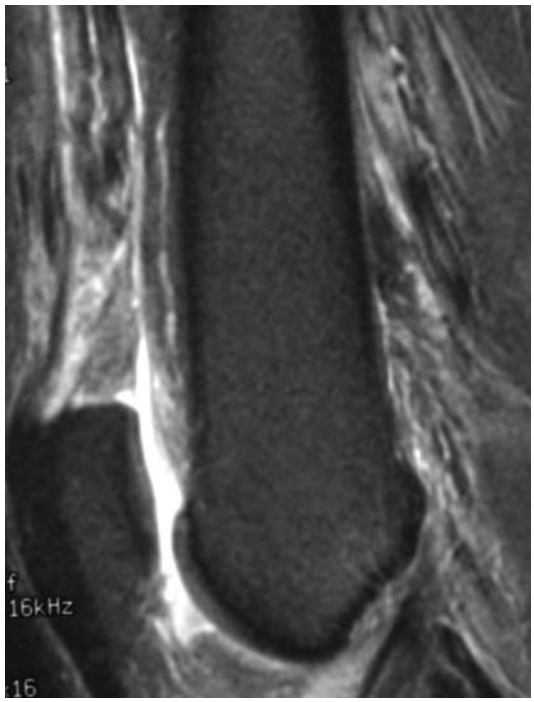

FIGURE 17-2. MRI scan of a patient with complete quadriceps tendon tear. (Courtesy of Wayne B. Leadbetter.)

raises and patella mobility exercises are commenced on postoperative day number one. Each week the brace is adjusted to allow an additional 10 to 20°, based on the repair strength. For chronic repairs a less aggressive rehabilitation protocol is employed.

Iliotibial Band Friction Syndrome

Iliotibial band (ITB) friction syndrome is caused by excessive friction between the ITB and the lateral femoral epicondyle. The condition is most frequently seen in distance runners and military recruits, but can occur with any activity requiring repetitive knee flexion and extension [18].

Anatomy and Function

The iliotibial tract originates proximally as a coalescence of fascial investments from the tensor fascia lata, the gluteus maximus, and the gluteus medius. In the thigh, the posterior aspect of the ITB attaches to the lateral intermuscular septum, thereby connecting the ITB to the linea aspera on the posterior femur. At the knee, the ITB has an anterior expansion, the iliopatellar band, and a posterior expansion to the biceps femoris [19,20]. The iliopatellar band attaches the anterior aspect of the iliotibial tract to the patella and stabilizes the patella against a medially directed force. The iliotibial tract crosses the knee to insert on Gerdy's tubercle just lateral and proximal to the tibial tubercle. The iliotibial tract is approximately twice as thick distally compared with the proximal fascia.

Proximally, the ITB assists the tensor fascia lata, gluteus maximus, and gluteus medius in abducting the thigh. Distally, the function of the ITB depends on the knee position. At knee flexion angles less than 20 degrees, the ITB lies anterior to the lateral femoral epicondyle and assists in knee extension. In contrast, the ITB lies posterior to the lateral femoral epicondyle at angles greater than 30 degrees of knee flexion.

Pathogenesis

The etiology of ITB syndrome has been attributed to friction between the deep layer of the ITB and the lateral femoral epicondyle.[18] The impingement zone occurs at 20 to 30 degrees of knee flexion where the ITB rubs against the lateral femoral epicondyle. This may occur in any athletic endeavor, especially distance running, which requires repetitive knee flexion and extension. In runners, it has been demonstrated that impingement occurs near foot strike, predominantly in the foot contact phase of the gait cycle, or in the deceleration phase of gait [21]. Since the gluteus maximus and tensor fascia lata are contracting eccentrically during this phase of running, the repetitive microstrains in the ITB may lead to degenerative changes. During downhill running, the knee flexion angle is decreased with more time spent in the impingement zone. Although controversial and unproven, running on a crowned road might cause the foot on the high side to excessively pronate, thereby causing injury [22,23]. ITB syndrome is most common in distance runners, but it has also been reported in cyclists and athletes involved in sports requiring repetitive knee flexion exercises [24–26].

Table 17-1. Risk factors for ITB syndrome

Genu varum
Foot pronation
Internal tibial torsion
Leg length discrepancy
ITB tightness
Training errors
Prominent lateral femoral epicondyle
Hip abduction weakness

Numerous factors may predispose the athlete to ITB syndrome (Table 17.1). Any malalignment of the lower extremity that increases the tension in the ITB or creates friction against the epicondyle may be present. These include genu varum, excessive pronation, a lateral condylar spur, or leg length discrepancy. It is unknown whether increased thickness of the ITB is a risk factor or a secondary phenomenon. Training errors may also be responsible for predisposing to ITB syndrome. Inexperienced runners who abruptly increase their weekly mileage have a higher incidence of ITB syndrome [23]. Hip abduction weakness may lead to ITB syndrome [27]. Fatigued runners with hip abduction weakness are prone to increased thigh adduction and tension on the ITB.

Clinical

The main symptom of ITB syndrome is pain or burning on the lateral aspect of the knee, 3 cm proximal to the joint line. Occasionally, the pain can radiate proximally along the ITB. Activities such as distance running or running downhill in which the knee repetitively flexes from 20 to 40 degrees may aggravate the symptoms. Initially, the symptoms subside shortly after exercising, but recur after subsequent inciting events. As the condition progresses, the symptoms may persist even during daily activities.

Physical examination reveals tenderness over the lateral femoral epicondyle, which is greatest at 30 degrees of knee flexion. In some patients, a rubbing or snapping sensation may be palpated as the ITB passes over the lateral femoral epicondyle. Pain may also be elicited over the lateral femoral epicondyle at 30 degrees of knee flexion when performing a single-leg deep knee bend.[18] The compression or Noble test is performed by flexing the knee to 90 degrees [28]. Pressure is applied to the lateral femoral epicondyle and the knee is gradually

FIGURE 17-3. Noble test. ITB syndrome is suggested if the patient experiences pain with pressure over the lateral femoral epicondyle at 30 degrees of knee flexion. (Courtesy of Wayne B. Leadbetter.)

extended. The test is positive if the patient complains of pain at 30 degrees of knee flexion, which reproduces the pain when exercising (see Figure 17-3). Tightness of the ITB should be evaluated by Ober's test [29]. Ober's test is performed by having the patient lie on the uninjured side with the unaffected hip and knee flexed. The examiner stabilizes the pelvis with one hand and holds the affected limb with the other hand. The involved knee is flexed to 90 degrees, and the hip is abducted and hyperextended. A tight ITB is present if the hip remains abducted and does not passively drop below an imaginary horizontal line.

In isolated ITB syndrome, there should be no knee effusion, instability, or a positive McMurray's test. Radiographs are typically normal. The differential diagnosis includes lateral meniscal pathology, biceps femoris or popliteus tendinopathy, early degenerative knee joint disease, stress fracture, and lumbar disc pathology. A local anesthetic injection is helpful in differentiating soft tissue pathology from an intra-articular derangement.

Although the diagnosis of ITB syndrome is primarily a clinical diagnosis, MRI may be helpful in confirming the diagnosis in refractory cases that are being considered for surgery treatment [30]. MRI is also helpful in excluding other diagnoses, such as a lateral meniscal tear. In one report, MRI was performed on 7 patients with ITB syndrome and compared with 10 age- and sex-matched control knees. Patients with ITB syndrome demonstrated a significantly thicker iliotibial band over the lateral femoral epicondyle. Thickness of the pathologic iliotibial band averaged 5.49 mm versus 2.52 mm in the control group. In addition, the MRI of 5 of the 7 affected patients revealed a small bursal fluid collection deep to the ITB in the region of the lateral femoral epicondyle.

The majority of patients with ITB syndrome respond to nonoperative management consisting of activity modification, anti-inflammatory medications, ITB stretching, gluteal strengthening exercises, and an orthotic for athletes with excessive foot pronation. An initial short period of activity restriction from running or cycling should be recommended. Stretching exercises are an important part of the rehabilitation and should be continued after return to activity (see Figure 17-4). Strengthening should focus on the gluteal muscles, and include side-lying leg lifts and single-leg step-down exercises [27]. In most patients symptoms resolve within 3 to 6 weeks. A corticosteroid injection into the underlying bursa is an option in refractory cases. Prior to return to activity, training errors need to be evaluated. For runners, this may require decreasing mileage, altering stride length, avoiding hills or periodic change of direction if running on a sloped surface. Recurrences can be avoided in cyclists by changing the seat height or the foot position with the use of spacers [24].

Only rarely is surgical intervention required after at least 6 months of nonoperative management [24,31]. Surgical excision of the affected ITB is preceded by an arthroscopic evaluation to exclude intra-articular pathology. The open procedure is performed through a longitudinal incision at the level of the lateral femoral condyle

FIGURE 17-4. Patient with ITB performing stretching exercises. (Courtesy of Wayne B. Leadbetter.)

with the knee placed in 30 degrees of flexion. The lateral condyle should be palpated for any bony spurs or osteochondromas, which may need to be excised. Next, a triangular piece of the posterior half of the ITB is resected. The leg is moved through a range of motion to ascertain that there is no further impingement. Postoperatively, the leg is immobilized in full extension for 1 week, and the patient is allowed to bear weight as tolerated. Thereafter, running is gradually resumed with full return to competition by 3 to 4 weeks. The surgical technique results in a high success rate [26,31,32].

Popliteus Tendon Disorders

Anatomy and Function

The popliteus musculotendinous unit instead of tendon–muscle unit runs along the posterolateral aspect of the knee. The tendinous portion arises from the lateral femoral condyle just anterior to the fibular collateral ligament insertion and deep to the knee joint capsule. It passes deep to the lateral collateral ligament termed the popliteal hiatus, which separates the lateral meniscus from the capsule [33,34]. The popliteus tendon has variable attachments to the lateral meniscus through fascicles [34]. As is crosses this area, a fold of synovium unsheathes the tendon. The popliteus unit then emerges from the capsule and inserts on the proximal posterior portion of the tibia through its muscle belly [35]. The popliteofibular ligament arises from the proximal fibula and joins the popliteus tendon just proximal to its musculotendinous junction [34]. The popliteofibular ligament provides significant mechanical resistance to posterior tibial translation, external rotation, and varus rotation [36]. Therefore, any injury to the popliteus tendon, especially avulsion, may indirectly affect posterolateral stability.

The function of the popliteus unit is twofold. First it acts as an internal rotator of the tibia [37]. Therefore, it assists in initiating knee flexion and early rotational "unlocking" from the tibia [38]. In addition, the popliteus functions as a secondary restraint in preventing posterior tibial translation on the femur. The popliteus is particularly active during downhill running. Pathologic conditions affecting the tendon include tendinopathy, subluxation and avulsion. Major damage to the popliteus unit may also occur in association with ligamentous injury to the posterolateral corner.

Popliteus Tendinopathy

Popliteus tendinopathy is an extremely uncommon cause of knee pain [39]. Athletes typically report the insidious onset of pain along the posterolateral portion of the knee. The pain occurs mainly during weightbearing when the knee is flexed between 15 and 30 degrees or during the early part of the swing phase. Often, patients report a recent increase in activity, especially downhill running, running on a banked surface, or backpacking downhill. The symptoms are typically aggravated by running and relieved with rest.

Physical examination reveals localized tenderness over the tendinous insertion of the popliteus at the lateral femoral condyle. Palpation of the affected tendon is most easily accomplished with the leg in a "figure-of-four" position. This allows easy detection of the lateral collateral ligament and of the adjacent popliteus tendon. Since findings may be absent at rest, having the patient run downhill prior to the physical examination may assist in localizing the pathology. Relief of symptoms after an injection of a local anesthetic into the tendon sheath may also be helpful. Unless there is concomitant intra-articular pathology, a joint effusion is typically absent. Plain radiographs are usually normal, but may show radiodensities in the area of the popliteus tendon in chronic cases. Lateral meniscal pathology is the most common diagnosis for patients presenting with lateral joint pain, and should always be included in the differential diagnosis. Other common causes of lateral knee pain include iliotibial band syndrome, discoid lateral meniscus, degenerative joint disease, lateral collateral ligament injury, osteochondritis dissecans, intra-articular loose body, occult cyst of the lateral meniscus, and proximal tibiofibular instability.

Treatment of popliteal tendinopathy depends on its chronicity [39]. Most cases are acute, and respond to a two-week course of rest and nonsteroidal anti-inflammatory drugs (NSAIDs). Upon return to activity, training modifications, such as avoiding downhill running, can help alleviate the stresses imposed on the popliteus tendon. Chronic cases usually require a more prolonged period of restricted activities, with or without a steroid injection into the tendon sheath. MRI may be indicated to exclude intra-articular pathology or tendon avulsion.

Popliteus Tendon Subluxation

Snapping of the popliteal tendon has been described in young athletes with no prior knee surgery [40,41]. The pathogenesis is unclear, but may be related to congenital structural abnormalities or tendon thickening. The onset of symptoms may be traumatic, hyperextension and/or varus mechanism, or spontaneous from repetitive motion. Snapping typically occurs between 20 and 40 degrees of knee flexion, and may require active knee motion or loading with varus stress for detection. In one report, the popliteus tendon subluxated posteriorly out of its groove with knee flexion past 40 degrees. In osteoarthritic individuals, the popliteal tendon has been reported to snap or sublux over a retained osteophyte or

the femoral component after total knee arthroplasty [42,43]. MRI and arthroscopy are helpful in excluding other entities, but reveal no specific findings in the snapping popliteus tendon syndrome. A trial of nonoperative management consisting of rest from aggravating symptoms and NSAIDs is often curative. In refractory cases, surgery may be warranted. Surgical options include tenodesis in the groove or popliteal tendon release. The tenodesis procedure is preferred in an athlete since it preserves the function of the popliteus unit. In patients with degenerative knee changes or a total knee replacement, treatment should include removal of the osteophyte or release of the popliteus tendon, either via an open or an arthroscopic approach.

Popliteus Tendon Avulsion

Isolated rupture of the popliteus tendon is extremely uncommon [44–47]. More commonly, concomitant injury to the posterolateral ligamentous complex occurs with acute or chronic posterolateral laxity. The mechanism reported is external rotation of the lower leg with the knee in slight flexion [46]. Patients with isolated avulsion of the popliteus tendon present with an acute hemarthrosis and lateral knee pain. Pain and weakness may be present during active internal rotation of the tibia against resistance or during passive external rotation of the tibia with the knee flexed 90 degrees [44]. A complete ligamentous examination should be performed to exclude injury to the lateral, posterior, or posterolateral structures.

Plain radiographs may demonstrate a small, faintly visible ossified fragment in the lateral gutter of the knee [45]. MR imaging is helpful in confirming the diagnosis and excluding concomitant injury. Arthroscopy is the recommended procedure for identifying and reattaching the osteochondral fragment. Reduction and fixation of the tendon restores the motor, ligamentous and proprioceptive functions of the popliteus complex.

Semimembranosus Tendinopathy

An uncommon, but often overlooked, cause of medial knee pain is semimembranosus tendinopathy (ST) [48]. Although tendinopathy may occur in any of the hamstring tendons at the knee, the semimembranosus is the most commonly affected. ST may occur as a primary phenomenon in endurance athletes or as a secondary, overuse, compensatory condition from a primary knee abnormality such as patellofemoral disorders [48].

Clinical Presentation

Patients with ST present with aching pain at the posteromedial aspect of the knee. The condition typically occurs in middle-aged endurance athletes. Symptoms are aggravated by strenuous activities such as prolonged jogging, climbing, or lifting. On examination, tenderness is localized to the posteromedial corner of the knee just inferior to the joint line. A thorough knee examination should be performed to exclude a primary disorder. The most commonly confused entity is a medial meniscal tear. Pes anserine bursitis is differentiated from ST by tenderness located more distally and anteriorly.

Secondary ST is treated after first addressing the primary knee disorder. The initial treatment for isolated or primary ST consists of rest, hamstring stretching exercises, and NSAIDs. The vast majority of patients respond to nonoperative management. For those who fail conservative management for at least 3 months, surgical intervention is appropriate. Prior to surgery, the diagnosis can be confirmed by a bone scan, which demonstrates increased tracer uptake at the posteromedial aspect of the proximal tibia. Alternatively, an MRI scan may also be helpful in confirming the diagnosis and excluding a medial meniscal tear.

Surgery should include diagnostic arthroscopy to exclude any intra-articular pathology. If arthroscopy reveals no intra-articular derangement, then an incision is made directly over the direct head insertion of the semimembranosus tendon. The semimembranosus tendon is dissected free from surrounding tissue and the sheath is opened. Any areas of necrosis or degenerative tissue should be excised. Several longitudinal tenotomies are performed. In addition, the insertion site is drilled with a small Kirschner wire to promote a healing vascular response. Tendon rerouting or suturing the semimembranosus to the posterior aspect of the medial collateral ligament has also been proposed if friction between the tendon and the tibial plateau exists. In one report, the results of surgery were good in 9 of 10 patients, and allowed return to sporting activities at an average of 12 months postoperatively [48].

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18
Patellar Tendinopathy and Patellar Tendon Rupture

Karim M. Khan, Jill L. Cook, and Nicola Maffulli

Introduction

Patellar tendon injuries constitute a significant problem in a wide variety of sports [1–4]. Despite the morbidity associated with patellar tendinopathy, clinical management remains largely anecdotal [5] as there have few well-designed treatment studies. This chapter will update the reader on management of 1) the patient with overuse patellar tendinopathy, and 2) the patient unfortunate enough to suffer the less common, but debilitating, condition of patellar tendon rupture.

Typical Clinical Scenario—Patellar Tendinopathy

In the patient with patellar tendinopathy, knee pain may arise insidiously. Those patients who recall when the pain began report that it started during one heavy training session or, less commonly, from one specific jump. In addition, they often remember a specific activity that seemed to make the pain worse. Pain is usually well localized to a small area over the anterior aspect of the knee region, and many patients have noticed tenderness at the inferior pole of the patella before they present for a medical examination.

Early in the clinical course, the patient's knee pain and discomfort may ease completely while exercising. In this case, the athlete often disregards the injury and does not seek treatment. With time and continued activity, however, pain worsens and limits sporting performance. Eventually, pain can develop during activities of daily living and can even be present at rest. Examination reveals tenderness at the junction of the patella and the patellar tendon. This clinical scenario has a number of names, including jumper's knee, patellar tendinopathy, patellar tendinosis, or patellar tendinitis. The preferred diagnostic term is patellar tendinopathy [6]. Palpation of the tendon attachment at the inferior pole of the patella has been the classic physical examination technique for detecting patellar tendinopathy, but mild tenderness at this site is not unusual in a normal tendon. Only moderate and severe tenderness is significantly associated with tendon abnormality as defined by ultrasonography. Thus, we suggest that mild patellar tendon tenderness should not be overinterpreted, and may be a normal finding in active athletes.

Patients with chronic symptoms may exhibit quadriceps wasting, most notably in the vastus medialis obliquus. Thigh circumference may be diminished, and calf muscle atrophy may be present. Testing the functional strength of the quadriceps may be done by comparing the ease with which the patient can perform 15 one-legged stepdowns on each leg. The athlete bends at the knee and then straightens again without letting the other foot touch the floor. Work capacity of the calf is assessed by asking the patient to do single-leg heel raises. Jumping athletes should be able to do at least 40 raises. It is important to monitor both the onset of fatigue and the quality of movement (e.g. control, as measured by wobbling), as either can be affected in the symptomatic limb.

In general, the clinical features of patellar tendinopathy are distinctive [7], and some authors have suggested that the diagnosis is straightforward [8]. Our clinical impression is that this is true in about three-fourths of the cases of patellar tendinopathy, but that in some cases patellofemoral joint syndrome and patellar tendinopathy may be difficult to differentiate, or the conditions may coexist.

Imaging Appearances

Magnetic resonance (MR) imaging and ultrasound (US) are the investigations of choice in the jumping athlete with knee pain (see Figures 18-1 and 18-2). Here we summarize the typical findings in a patient with patellar tendinopathy and we discuss the clinical utility of the imaging modalities.

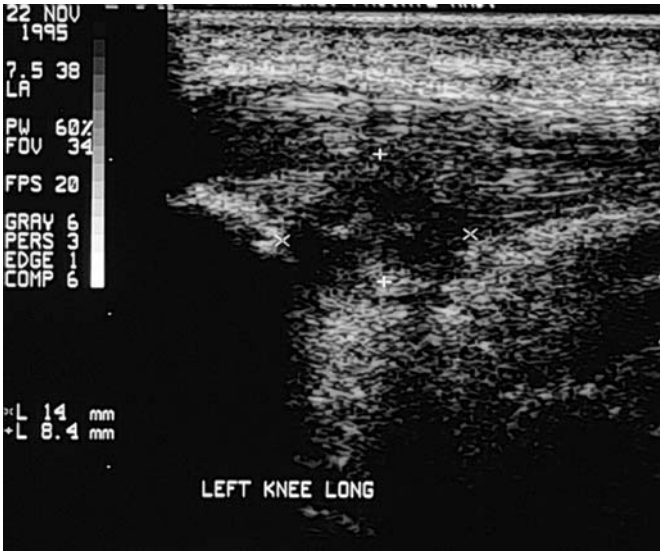

FIGURE 18-1. Longitudinal ultrasound scanning of a 25 year old basketball player with patellar tendinopathy. Note the area of hypoechogenicity.

MR Imaging

The abnormal patellar tendon contains an oval or round area of high signal intensity on T1 and T2 and the proton density–weighted images at the tendon attachment, or a focal zone of high signal intensity in the deep layers of the tendon insertion [9–11] (Figure 18-1). Tendons with patellar tendinopathy have increased anteroposterior diameter in the affected region [9,11,12].

The T2 weighted sequences (particularly the T2 weighted GRE sequences) have better sensitivity than the T1 weighted protocols [9,10,13]. However, the T1 weighted signal can image most cases of patellar tendinopathy.

In clinical practice, MR scans can identify the exact location and extent of tendon involvement, and help exclude other clinical conditions such as bursitis and chondromalacia [11]. Surgeons use MR to assess the severity of patellar tendon disease and determine how much tendon to excise [9,11].

Disadvantages of MR include cost, and the slow, often incomplete resolution of signal changes after surgical intervention [14,15]. Whether MR abnormalities occur in asymptomatic patellar tendons has not been examined, but other tendons contain high signal abnormality on MR in nearly a quarter of young volunteers [16].

Abnormal signal without change in size must be interpreted with caution, as the normal patellar tendon has a range of appearances due to technical factors and intrinsic fiber differences [17]. In particular, the "magic angle" phenomenon can result in false positive high signal intensity on GRE T2 weighted images of normal tendon [10,18,19].

Ultrasonography (c)

Sonographic studies in athletes with the clinical features of patellar tendinopathy should include both knees using high-resolution, linear array, 10 or 12 mHz ultrasound transducers. It is vital that the examination is performed with the probe exactly perpendicular to the tendon to avoid a false positive image due to artifactual hypoechogenicity [20]. Sonographic appearances in jumper's knee reveal a focal hypoechoic area (Figure 18-2) combined with various amounts of swelling of the surrounding tendon. Hyperechoic regions within the tendon correspond with dystrophic ossification on histopathology [10].

A proportion of asymptomatic athletes have sonographic hypoechoic regions in their patellar tendons. Among volleyball players, 24% of asymptomatic knees contained patellar tendons with hypoechoic regions on US [21]. Similarly, 15% of basketball players with no past history of knee pain had abnormal tendon morphology on US [22]. Comparable findings have been reported in

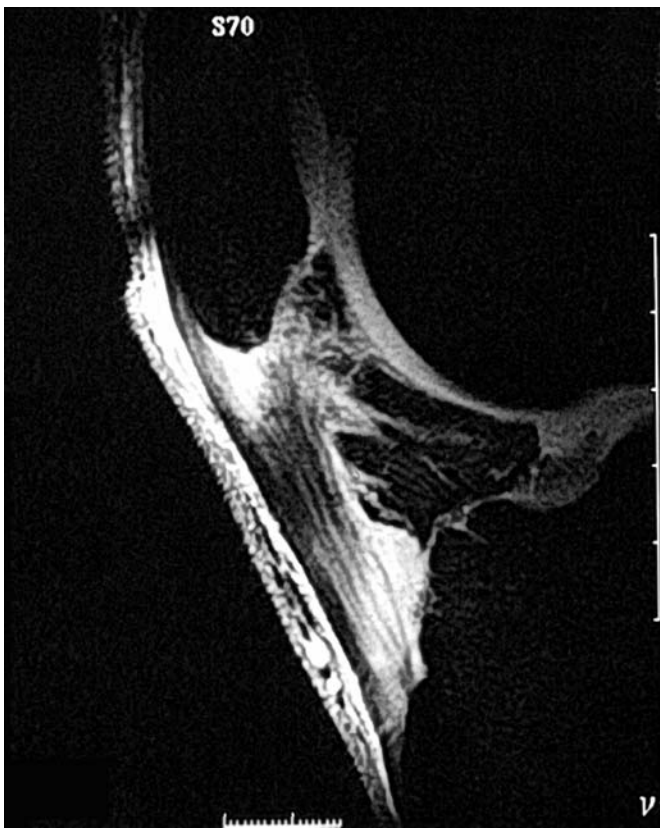

FIGURE 18-2. The same patient at MRI scanning.

asymptomatic recreational athletes [23]. Furthermore, longitudinal studies found that hypoechoic US regions did not predict subsequent development of symptoms in athletes [24], but conferred relative risk of patellar tendinopathy in 16- to 18-year-old basketball players [25]. These data suggest prudence when considering ultrasound appearance as a guide to prognosis and management [26]. A sonographic hypoechoic region is not, of itself, an indication for surgery [24,25,27]. Surgeons have used US to accurately locate the area of tendinopathy to allow correct placement of the scalpel blade when performing multiple percutaneous longitudinal tenotomies [28].

Conservative Management of Patellar Tendinopathy

Given the degree of morbidity associated with chronic tendon problems, and the extent of knowledge in certain areas of medical treatment, there is a surprising lack of scientific rationale for tendon treatment [1]. Conservative and operative treatments of tendinopathies vary considerably among surgeons and across countries. Unfortunately, "there is little scientific evidence for the majority of treatments proposed and used for chronic tendon problems [14]." Thus, the treatment outlines suggested below are, at best, "empirical." We discuss conservative management of the athlete with patellar tendinopathy under 5 broad headings: 1) decreasing load on the tendon; 2) eccentric strengthening; 3) cryotherapy and physical modalities including ultrasound and laser; 4) remedial massage; and 5) pharmacological management.

Decreasing Load on the Tendon

Load can be reduced on the tendon by reducing overall activity, and by improving the efficiency of lower limb biomechanics to protect the patellar tendon. Athletes who present with patellar tendinopathy for the first time have their best opportunity to make a full recovery by resting from competition and undergoing thorough rehabilitation before returning pain-free to their sport. This approach is advocated even in elite regular competitions (e.g. an NBA season, premier league soccer, world league volleyball), but a compromise may be necessary immediately prior to one-off tournaments such as world championships or Olympic games. Nevertheless, this conservative approach is often unacceptable to players (who have little pain) and to coaches (who are paid to have short-term goals). A poor alternative may be a period of rest taken at the end of a season, but by that time the tendon is likely to have a much greater degree of tendinosis. In jumping sports, forces generated in landing are substantially greater than those that produce the jump [29]. Therefore, correcting biomechanics improves the energy-absorbing capacity of the limb, both at the affected musculoskeletal junction and at the hip and ankle. The ankle and calf are critical in absorbing the initial landing load, and any functional compromise of these structures increases the load transmitted to the knee [29]. About 40% of landing energy is transmitted proximally [30]. Thus, the calf complex must absorb a major portion of the load that would otherwise be transmitted proximally to the patellar tendon–quadriceps complex. Compared with flat-foot landing, forefoot landing generates lower ground reaction forces; if this technique is combined with a large range of hip or knee flexion, vertical ground reaction forces in landing can be reduced by a further 25% [31].

These data suggest that the practitioner should assess the patient's static alignment and functional biomechanics [32]. Anatomic variants that predispose to patellar tendinopathy are listed in Table 18-1. Some anatomic abnormalities, such as pes planus, may be evident during static assessment, but others, such as excessively rapid pronation, may only be evident during dynamic evaluation. Shoe orthoses are one method of correcting some biomechanical faults. Some physicians, but not us, routinely recommend knee braces.

Biomechanical abnormalities arise from functional as well as anatomic abnormalities. Low flexibility of the quadriceps, hamstrings, iliotibial band, or calf has the potential to restrict range of motion at the knee and ankle joints and is likely to increase the load on the patellar tendon. Hamstring tightness, detected by a decreased sit-and-reach test, is associated with increased prevalence of ultrasonography-proven patellar tendinopathy [25]. Weakness of the gluteal, lower abdominal, quadriceps, and calf muscles leads to fatigue-induced aberrant movement patterns that may alter the forces acting on the knee. It is imperative that proximal and distal muscle groups be assessed in patients with chronic patellar tendinopathy.

Table 18-1. Anatomical characteristics associated with patellar tendinopathy

Limb or joint	Anatomical characteristic
Foot	Excessive range of pronation, excessively fast pronation (even within a normal range), pes planus, rigid cavus foot, poor dorsiflexion (e.g., due to anterior impingement syndrome)
Knee	Hyper- or hypomobile patella leading to poor mechanism of patellofemoral movement, tight band between illiotibial band and patella
Thigh	Tight iliotibial band
Hip	Coxa vara, femoral anteversion

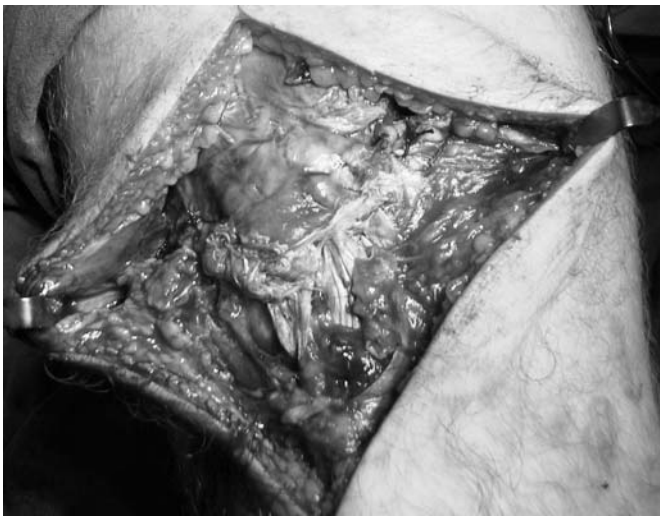

FIGURE 18-3. Typical appearance of ruptured patellar tendon at surgery.

Eccentric Exercise Protocol

Eccentric strengthening has long been recognized as the keystone to successful management of tendinopathies [33,34]. Well-designed studies have demonstrated the efficacy of strengthening as a treatment for both Achilles and adductor tendinopathy [35–37], but there are few published studies of strengthening for the patellar tendon [33,38].

Eccentric loading of the patellar tendon may well be essential to promote clinical recovery [33,39,40]. The key exercise was a drop squat from standing to about 100 to 120 degrees of knee flexion. Patients perform 3 sets of 10 repetitions per session (one session daily) [33,40]. The proposers of this treatment program emphasized the principles of training specificity, maximal loading, and progression [41,42]. In basketball and volleyball players, specificity is achieved by using jumping activities as the rehabilitative exercise. Maximal loading occurs when patients feel pain in their tendons during the third set of 10 repetitions. Progression is achieved by increasing the speed of movement or by increasing the external resistance, again using pain as a guide. Ice is used to cool the tendon after the eccentric training.

Some authors [41,42] contend that athletes often do not need to refrain from sport during the strengthening program, and that athletes become asymptomatic after 6 to 8 weeks exercising [33]. Under close clinician supervision to adjust the program as needed [41,42], this regimen brought complete relief to 30% of patients and marked decrease in symptoms to a further 64% [33]. The remaining 6% had worsening symptoms. A randomized pilot study found a nonsignificant trend for eccentric strengthening to be superior to a concentric training program in patellar tendinopathy [38]. Given the natural history of patellar tendinopathy, these results are encouraging.

Prescribing Eccentric Exercise: Practical Issues

Therapists often have concerns as to when and how they should begin a strengthening program. Even athletes with severe patellar tendinopathy should be able to begin some exercise, at the very least standing calf strength and isometric quadriceps work (see Figure 18-4). On the other hand, the athlete who has not lost appreciable knee strength and bulk can progress quickly to the speed part of the program. Table 18-2 presents a strength program embracing the activities and timelines that our clinical experience has shown to be effective.

Both pain and the musculotendinous unit's ability to do work should guide the amount of strengthening activity. If pain is a limiting factor, then the program must be modified so that the majority of the work is relatively pain free, and does not cause delayed symptoms, commonly pain the morning after exercise.

A subjective clinical rating system such as the Victorian Institute of Sport Assessment (VISA) score [43–45]

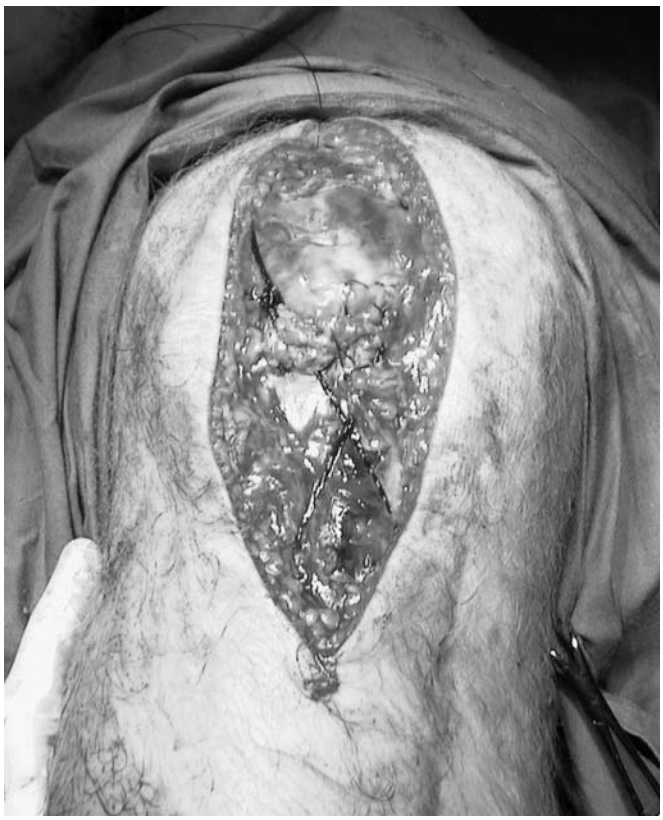

FIGURE 18-4. Repaired patellar tendon with end-to-end suture and figure-of-eight reinforcement with a figure-of-eight strong absorbable material passed through a tunnel in the anterior tibial tuberosity and over the superior pole of the patella.

Table 18-2. Outline of strengthening program for management of patellar tendinopathy

Timing	Type of overload	Activity
0–3 months	Load endurance	Hypertrophy and strengthen the affected muscles, focus attention on the calf as well as the quadriceps, gluteals
3–6 months	Speed endurance	Weightbearing speed-specific loads
6+ months	Combinations dependent on sport (e.g., load, speed)	Sports-specific rehabilitation

(a numerical scale for assessing the severity of jumper's knee) helps both the therapist and the patient to measure progress, and it allows early detection of any worsening of symptoms.

If pain is under control, then the practitioner supervising the program should monitor the control and quality with which the patient performs the exercises. Progression to the next level of the program should only be performed if the previous work load is easily managed, pain is controlled, and function is satisfactory.

Because athletes with patellar tendinopathy tend to "unload" the affected limb to avoid pain, they commonly have not only weakness, but also abnormal motor patterns that must be reversed. Strength work must progress to single leg exercises, as bilateral exercises only offer options to continue to unload the tendon. Some physicians and therapists maintain that quadriceps-only exercises such as leg extensions have a place in the rehabilitation of patellar tendinopathy, specifically to load the quadriceps exclusively, not allowing the calf and glutei to "take over" the exercise. Similarly, we have found that squats performed on a 30-degree decline board are effective in reducing the influence of the calf group in retarding knee flexion such as occurs in a normal squat done with the heels fixed. The therapist can help the patient progress by adding load and speed to the exercises, and then endurance can be introduced once the patient can do these exercises well. After that, combinations such as load (weight) and speed, or height (e.g. jumping exercises) and load can be added. These end-stage eccentric exercises can provoke tendon pain, and are recommended only after a sufficiently long rehabilitation period and when the sport demands intense loading. In several sports it may not be necessary to add height to the rehabilitation program at all, whereas in some sports (volleyball, for example), it is vital.

The exercise program must help to correct aberrant motor patterns such as stiff landing and pelvic instability. For example, athletes must learn to perform weightbearing exercises within a functionally required range with appropriate pelvic control.

Failure in rehabilitation strength programs can stem from many sources. They include too rapid a progression of rehabilitation; inappropriate loads (not enough strength or speed work, eccentric work too early or aggressively, insufficient single leg work); too many electrotherapeutic modalities; and lack of monitoring patients' symptoms during and after therapy. Rehabilitation and strength training must also continue through the return to sports, rather than ending immediately on return. Finally, plyometrics training can be performed inappropriately, not tolerated, or done unnecessarily.

Cryotherapy and Physical Modalities

To control initial tissue response to tendon injury, most clinicians advise rest, cryotherapy and anti-inflammatory medication (see below). Cryotherapy is thought to act by decreasing blood flow and metabolic rate, thereby limiting tissue damage. Electrical modalities that have been used in patellar tendinopathy include ultrasound, heat, interferential therapy, magnetic fields, pulsed magnetic and electromagnetic fields, transcutaneous electrical nerve stimulation (TENS), and laser. The background to the use of these modalities is explained elsewhere [1,39]. Their true effects remain unknown. Whether or not modalities are beneficial in tendinopathy is an area of disagreement. One of us (NM) generally includes cryotherapy, laser and magnetic fields, and pulsed magnetic and electromagnetic fields as part of treatment [39].

Remedial Massage

Remedial massage aims to decrease load on tendons by improving muscle stretch. Deep friction massage may activate mesenchymal stem cells to stimulate a healing response [45].

Pharmacotherapy

The main pharmaceutical agents used to treat patellar tendinopathy have been nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. After discussing these, we review the data regarding novel agents for treating tendinopathies.

Although the biological basis for using NSAIDs in tendinopathies is not obvious [1,46], these drugs are undoubtedly the most commonly used symptomatic therapy. In the only double-blind, placebo-controlled study of NSAIDs in tendinopathy, piroxicam did not benefit patients with Achilles tendinopathy [47]. A study of topical ketoprofen in patellar tendinopathy showed that the drug reached target tissue, but the authors did not assess clinical outcome [48]. Although the use of "anti-inflammatory" medication seems paradoxical in a degenerative condition, NSAIDs act in ways beyond their well-known anti-inflammatory mode [49,50]. For

example, in human cartilage *in vitro*, some NSAIDs stimulate and some inhibit glycosaminoglycan synthesis [51]. If this also proves to be the case *in vivo* in tendons, it would provide a mechanism whereby NSAIDs could influence extracellular matrix. Thus, it would appear premature to rule out any potential benefit of this class of medication merely because tendinopathy is not an inflammatory condition.

Injection and infiltration of corticosteroids by means such as iontophoresis has a dramatic effect on symptoms arising from inflamed synovial structures [52]. However, the role of corticosteroids in management of tendinopathy remains controversial [53,54]. A key point is that, after injection, a tendon is at increased risk of rupture until appropriate strengthening has been undertaken [55]. Recently, aprotinin has been trialed in the management of patellar tendinopathy [56]. Aprotinin is a polyvalent inhibitor of the proteases—collagenase, elastase, metalloprotease, kallikrein, plasmin, and cathepsin C [57]. At least in the short term, aprotinin (2 to 4 injections of 62,500 IU with local anesthetic in the paratendinous space) seems to offer better chances of pain relief than corticosteroids. However, patients with an insertional tendinopathy fared less well than those with tendinopathy of the main body of the tendon. As aprotinin is an anti-inflammatory agent, its administration is probably only warranted in athletes with relatively short duration of symptoms.

Using a combination of all of the above conservative management modalities, 33 of 42 athletes who presented to a specialist clinic within a few weeks from the onset of symptoms were able to return to their sport 6 months after the first visit. In the 9 patients presenting with Blazina's Stage 3 disease, conservative measures failed, and surgery was necessary [58].

Surgical Management

Patellar tendon surgery [26,59–67] is generally performed when the patient has not improved with at least 6 months of conservative management. A variety of surgical methods for treatment of jumper's knee have been described [68]. These include: drilling of the inferior pole of the patella; resection of the tibial attachment of the patellar tendon with realignment [69]; excision of macroscopic degenerated areas [61,62]; repair of macroscopic defects [65]; scarification (i.e. longitudinal tenotomy/tenoplasty of the tendon) [70]; percutaneous needling [71]; percutaneous longitudinal tenotomy [28]; and arthroscopic debridement [72]. Surgical technique is based on surgeon's opinion and experience, as the pathophysiology of patellar tendinopathy is not known.

Patellar tendon surgery has a rather unpredictable outcome. A review of 23 papers found that the outcomes of surgery varied between 46% and 100% [73]. In the 3 studies that had more than 40 patients, authors reported combined excellent and good results of 91%, 82%, and 80% in series of 78, 80, and 138 subjects, respectively. The mean time for return to preinjury level of sport varied from 4 months to greater than 9 months. A long-term study of outcome in patients who underwent open patellar tenotomy for patellar tendinopathy showed that only 54% were able to return to previous levels of sport activity [72]. In 2 prospective studies that evaluated time to return to sport, most subjects required more than 6 months, and often 9 months, to return to full sporting competition [15,28]. Unfortunately, several factors confound the analysis of outcome of surgery [73]. Surgeons differ in their diagnostic criteria, selection of cases for surgery, the actual operation performed, as well as in their postoperative protocols. Different types of surgery result in differences in the amount of bone either excised or drilled from the inferior pole of the patella, the margin of normal tissue excised around the macroscopically degenerative tissue, the use or avoidance of longitudinal tenotomies, and the type of closure, if any, of the tendon after surgery. Intersurgeon technical ability is another major factor whose influence has never been studied.

Recently, we have shown that the scientific methodology behind published articles on the outcome of patellar tendinopathy after surgery is poor, and that the poorer the methodology the higher the success rate [73]. Obviously, improving study design would provide clinicians with a more rigorous evidence-base for treating patients who have recalcitrant patellar tendinopathy.

Conclusions

Patellar tendinopathy is a degenerative, not an inflammatory, condition of the patellar tendon, most likely a result of excessive load bearing. Clinical assessment is the key to diagnosis, although the presence of US or MR abnormalities increases the likelihood that the patient's symptoms arise from the patellar tendon. Imaging appearances should not dictate management, which, for the time being, remains based on clinical experience, rather than scientific rationale.

A variety of management modalities exist, including correcting perceived underlying biomechanical problems, local physical modalities such as ice, and, when the patient is pain free, a graduated strengthening program emphasizing functional exercises including eccentric training. Eccentric training appears most promising, but well-designed controlled studies are awaited. To prescribe exercise effectively requires thorough assessment of the patient's functional capacity and a skillful approach to gradually increasing the demand that the athlete imposes on the tendon.

Clinical experience suggests that, in some patients, peritendinous corticosteroid or aprotinin infiltration may be warranted as an adjunct to other appropriate treatments. Surgery is indicated after a 6- to 9-month trial of appropriate conservative management. Open patellar tenotomy is the conventionally accepted surgical treatment of insertional patellar tendinopathy, but often requires 6 to 12 months rehabilitation. Arthroscopic debridement has been proposed, and, although randomized controlled trials are lacking, this procedure may permit earlier return to sport than traditional open surgery, even though both techniques have an equal success rate at 12 months [72].

Rupture of the Patellar Tendon

Rupture of the patellar tendon is relatively infrequent. It is usually seen in active patients around the age of 40 [74], but, with the increased participation in sports of all ages, it is not uncommon to see this injury in older patients.

The vast majority of ruptures of the patellar tendon are unilateral, although bilateral ruptures have been described [75]. In these instances, a rupture may occur during less strenuous, nonathletic activity [76].

Biomechanics of the Extensor Mechanism

During active knee extension, forces generated in the quadriceps muscle complex are transferred via the patellar tendon to the proximal tibia. Forces generated in the patellar tendon while ascending stairs are approximately 3.2 times body weight [77], and the force necessary to cause a patellar tendon rupture in a weight lifter approached 17.5 times body weight [78]. The force required to rupture a tendon weakened by systemic disease is much lower, although no data are available.

Etiopathogenesis of Patellar Tendon Rupture

Tensile overload of the extensor mechanism usually leads to a transverse fracture of the patella, which is considered the weakest link [75]. Patellar tendon rupture due to indirect trauma is probably the end stage of chronic tendon degeneration [79]. In a study of 53 patellar tendons, all the ruptured tendons exhibited pathologic changes, whereas such changes were detected in only one third of intact tendons from age-matched control subjects [80].

In a review of 13 athletes with chronic jumper's knee resulting in tendon failure, 10 sustained a patellar tendon rupture (one bilateral), and 3 had a quadriceps tendon rupture [79]. Patients younger than 25 presented more severe symptoms of patellar tendinopathy before rupture, and older patients complained of less severe symptoms. Probably, more advanced degeneration is required to critically weaken a younger tendon. Less advanced microtrauma, combined with the natural increase in stiffness resulting from ageing, probably lead to rupture in older athletes. Patients with preexisting systemic disorders, such as systemic lupus erythematosus, rheumatoid arthritis, chronic renal failure, and diabetes mellitus, are susceptible to patellar tendon ruptures during non-strenuous activity [75]. Patellar tendon ruptures are also seen in patients on long-term systemic corticosteroids [81], who are at greater risk of bilateral ruptures [75,81]. A rupture may also occur after local corticosteroid injection close to the tendon for chronic patellar tendinopathy [82]. In the series by Kelly et al. [79], 8 of 13 patients treated for jumper's knee received 2 to 3 corticosteroid injections in or around the patellar tendon before rupture.

Patellar tendon rupture has been reported after some surgical procedures that disturb the midsubstance or insertion sites of the patellar tendon, such as total knee arthroplasty [83]. In these instances, no single technique consistently guarantees good results. Primary repair, possibly reinforced with autogenous hamstrings, and extensor mechanism allografts have been advocated [83]. Primary suturing of the torn tendon ends should be attempted if adequate local tissue is present. Allografts may be considered at a later stage as a method of salvage.

Patellar tendon rupture can ensue after anterior cruciate ligament reconstruction performed with use of the central third [84]. Proximal tendon rupture or avulsion of the distal pole of the patella usually occurs when patients are too active before complete healing of the graft harvest site. Primary tendon repair is the management of choice, and the rupture normally does not interfere with the result of the anterior cruciate ligament reconstruction.

History and Physical Examination

Normally, the patient has sustained a forceful eccentric contraction of the knee extensors against the full body weight, placing the knee in a flexed position (e.g. landing after a rebound, tripping up the stairs). Sudden pain with an associated tearing or popping sensation is experienced. Unassisted weightbearing is impossible. The patient usually presents with a tense hemarthrosis and inability to bear weight on the involved leg. Intra-articular injuries must be excluded. The most important sign in patellar tendon ruptures is the lack of active extension of the knee with inability to maintain the passively extended knee against gravity. If the rupture extends completely through the tendon and the retinacula, active extension is lost completely. Less commonly, if the rupture involves only the tendon, and most of the retinacular fibers remain intact, some extension will be possible [74]. A short while after the injury, there is often a palpable gap at the level

of the rupture, and the patella may be proximally displaced compared with the contralateral side. Passive knee flexion is markedly diminished because of pain.

When the diagnosis is delayed, the tendon defect may be obscured by consolidation of the haematoma and early scar formation. Some active knee extension can be possible, but an extensor lag will be evident. Quadriceps atrophy and proximal migration of the patella are usually seen. Weight bearing may be possible, but often with a forward flinging motion of the affected leg in the swing phase and feelings of knee instability during single-leg stance [85]. Stair climbing and rising from a chair are very difficult.

Imaging

Plain Radiography

Plain radiographs are cost-effective and are sufficient in most cases. On the lateral view, a patella alta is identified. One or more bone fragments may be seen if the tendon was avulsed.

Ultrasonography

High-resolution ultrasonography is effective to image the patellar tendon in both acute and chronic injuries [86]. In acute ruptures, hypoechogenicity is noted over the entire thickness of the tendon. In chronic tears, thickening of the tendon at the rupture site is seen, with disruption of the normal echo pattern.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an expensive way of diagnosing acute and chronic patellar tendon ruptures [87]. The normal patellar tendon demonstrates a homogeneous low signal intensity throughout its course on proton-density images. The anterior and posterior margins are well defined. In patellar tendon ruptures, there is discontinuity of tendon fibers, waviness of the ends of the tendon, and an increase in signal intensity on sagittal T2 weighted images. Hemorrhage and edema may also be seen posteriorly to the infrapatellar fat pad. We do not recommend MRI to evaluate acute patellar tendon ruptures. However, it may be helpful in patients with neglected tears, when the diagnosis is uncertain or when associated intra-articular injuries are suspected.

Classification

Various authors have tried to classify patellar tendon ruptures on the basis of the location, configuration, and duration of the rupture. Some authors [88] grouped patellar tendon ruptures into 3 categories according to the location of the disruption: distal pole of the patella, tendon midsubstance, or tibial tubercle. Others [79] classified the ruptures according to the morphology of the tears: transverse, Z type (medial patellar avulsion with a lateral tubercle avulsion), and inverted-U type (medial and lateral portions ruptured from the tibial tubercle and the midportion avulsed from the patella). No study has been able to show a correlation between the type of rupture and the method of repair undertaken or the clinical outcome.

When bilateral ruptures were classified into midsubstance tears or tendon avulsions from the proximal or distal end, most cases of midsubstance rupture occurred in patients with chronic diseases. Proximal or distal tendon avulsions were usually seen in healthy patients with no systemic or local disease. Again, there is no correlation between the type of tear and the clinical result [81].

The only classification correlated with outcome takes into account the time between injury and repair. When repaired patellar tendon ruptures were divided into 2 categories based on the interval between injury and repair, immediate repair and delayed repair performed more than 2 weeks after injury [74], immediate repair was shown to be beneficial. Primary tendon repair was usually feasible in patients operated on immediately, whereas preoperative patellar traction and fascia lata autografts were often required for patients with a neglected rupture. Patients who underwent a delayed repair had greater loss of flexion and higher incidences of persistent quadriceps atrophy and strength loss.

Management

Conservative management is ineffective.

Immediate Repair

Surgical repair to restore the extensor mechanism should be performed as soon after the injury as possible both in athletic and nonathletic patients, regardless of their age. A number of methods for immediate surgical repair have been described. We perform simple end-to-end, Bunnell-type repair with the use of heavy absorbable sutures through transosseous tunnels with a reinforcing cerclage suture of absorbable suture material or tape [79,81,88–91] (see Figures 18-3 and 18-4). The repair is performed under tourniquet control. A longitudinal midline incision is made from the midpatella to the tibial tubercle. Full-thickness skin flaps are lifted to expose the tendon and the adjacent retinacula. The tendon ends are debrided. If the injury involves an avulsion off the distal pole of the patella or tibial tubercle, the tendon is cleared of loose bone fragments too small for internal fixation. The medial and the lateral extent of the retinacular tear are identified, and repaired. Three or 4 heavy absorbable sutures are passed through a transverse hole approximately 1 cm posterior to the tibial tubercle, brought prox-

imally, and passed transversely through the quadriceps tendon close to the superior border of the patella in a figure-of-eight fashion. Tension is applied to the sutures, which are then clamped but not tied. In the North American literature, it is recommended that a lateral radiograph of the knee be obtained at this stage to assess the patellar height compared with that on preoperative radiographs of the contralateral knee. However, residual articular incongruity alone is not be the cause of persistent anterior knee pain in patients who undergo repair. We prefer to flex the knee to 90 degrees, test the tension of the sutures, adjust them as required, and tie them. The wound is closed in layers, and the knee is placed in a well-padded dressing, without using braces.

Postoperative Rehabilitation

Isometric quadriceps- and hamstring-strengthening exercises are begun on the first day after surgery, and we allow protected weightbearing with crutches from the second postoperative day. Active flexion and extension of the knee are started 2 weeks after the operation. Weightbearing progresses to full weightbearing without crutches by 4 to 6 weeks postoperatively, if good quadriceps control is shown.

Although isokinetic rehabilitation is very much in fashion, we prefer to undertake functional rehabilitation with isoinertial exercises, gradually progressing to a sport-specific functional rehabilitation program. Resumption of strenuous athletic activity is allowed 4 to 6 months postoperatively, when the patient should have a full range of knee motion and at least 85% of the strength of the contra-lateral extremity.

Delayed Repair

Simple end-to-end suture is difficult when the repair has been delayed more than 6 weeks [74,85,92]. The longer the delay between injury and repair, the greater the likelihood of quadriceps contracture and proximal patellar migration. Fibrous adhesions may form between the patella and the femur. Distally, the ruptured tendon ends retract and become embedded in scar tissue, and calcific intratendinous deposits may develop. Patients with a neglected rupture of several months' duration who present with superior patellar migration, loss of passive patellar mobility, and lack of full passive knee motion may require preoperative patellar traction [74]. This can be accomplished over several days to a few weeks with a 2 kg weight through a Steinmann pin placed transversely through the midportion of the patella. Lateral radiographs of the knee are taken weekly until the patella has been returned to its anatomical position.

Primary repair combined with autogenous graft augmentation using the fascia lata [74] or hamstring tendons [92] has been described, and should be attempted if sufficient tendon is left for repair. Carbon fibers [93] and nonabsorbable tape suture materials [74] have also been advocated. Achilles and patellar tendon allografts have also been used, mostly in salvage situations [94]. Allografts allow early, vigorous rehabilitation. However, there is a risk of disease transmission.

Rehabilitation after a neglected rupture is considerably more conservative than that after repair of a fresh rupture. A brace is used for 6 weeks, during which time gentle passive exercises are performed, followed by active range of motion exercises to regain full extension. Closed manipulation of the knee is occasionally required to increase the range of motion of the knee.

Results

Most patients undergoing early primary repair achieve nearly full return of knee motion and extension strength, although persistent quadriceps atrophy is common [74,88]. The only factor that appears to correlate with clinical outcome is the timing of repair. Patients who undergo delayed repair have greater persistent quadriceps atrophy.

No large series evaluates the results of reconstruction of a neglected rupture [85,92,94]. Patients who require pre-operative traction and the use of autogenous or allograft tendons may have a worse result than patients with sufficient tissue for an end-to-end repair [74].

Complications

Decreased quadriceps strength and loss of full knee flexion are the most common complication after a patellar tendon repair. Aggressive postoperative rehabilitation, with early range of motion and quadriceps exercises, should be implemented. Manipulation under anaesthesia may be considered if 120 degrees of flexion are not achieved by the second post-operative month. Arthroscopic debridement can be considered to achieve the last few degrees of extension if these are lacking despite appropriate rehabilitation. Quadriceps atrophy does not compromise the final return of strength, both subjectively and objectively [74,88].

Hemarthrosis necessitating either aspiration or formal drainage occasionally develops, and the use of a suction drain should be considered. Wound infection or skin dehiscence may occur, usually over the distal aspect of the wound, where the skin is relatively thin. This complication can be avoided by placing the skin incision lateral to the tibial tubercle, and by imparting less tension at the suture line. Rerupture is occasionally seen in patients who attempt to return to running or jumping activities before complete healing of the repaired tendon [74]. Revision is usually successful in reestablishing knee

motion and strength, as long as the repair is performed early. When the repair has been reinforced with a cerclage wire, wire breakage may occur. The wire may need to be removed because of skin irritation and wire extrusion. For this reason, we use absorbable sutures, rather than metallic wire, as the reinforcing material. Patella baja may occur, with resultant motion loss and the risk of patellofemoral degeneration if excessive tension on the sutures causes inaccurate coaptation of the tendon ends.

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19
Hindfoot Tendinopathies in Athletes

Francesco Benazzo, Mario Mosconi, and Nicola Maffulli

Introduction

The hindfoot presents pathologies due to functional overload and, less frequently, due to macrotraumas. The overload pathologies of the hindfoot are part of "posterior carrefour syndrome" (PCS) [1], which includes bony, tendinous, capsular, and neural pathologies:

- The posterior portion of the talus (tuberculum, os trigonum)
- The third malleolus of the tibia
- The posterior portion of the calcaneus
- The Achilles tendon
- Peroneal tendons (longus and brevis)
- Tibialis posterior tendon and/or nerve
- Flexor digitorum and flexor hallucis tendons
- Plantar fascia

Functional Anatomy and Biomechanics

Functionally, the hindfoot is defined by a coronal plane passing through the neck of the talus: all the structures which lie behind this plane are included in the posterior region of the foot.

The subfascial layer contains posteriorly the Achilles tendon and its bursae. Laterally, there are the peroneal longus and brevis tendons. The tendons of tibialis posterior, hallucis longus and digitorum longus lie medially. The plantar fascia is contained by the extension of the crural fascia onto the calcaneal body.

The hindfoot is not an isolated structure, and it must be considered as a whole with the leg and with the foot. The foot absorbs impact at the time of initial ground contact, and provides a rigid lever for toe off. All these functions occur because of the ability of the ankle and subtalar joints to transmit and translate the vertical and rotational forces passing through the hindfoot.

The Ankle Joint

The main function of the ankle joint is dorsoplantar flexion. Although it was considered a pure hinge joint with a fixed axis in the frontal plane, the joint axis changes inclination close to the neutral position between plantar and dorsiflexion. More recently, the ankle joint has been compared with an ellipsoid joint with two degrees of freedom thanks to the variation of the rotational axis [2,3]. The range of motion of the ankle joint varies from 13 to 33 degrees of dorsiflexion and from 23 to 56 degrees of plantar flexion.

The Subtalar Joint

The subtalar joint is formed by the inferior surface of the talus and the superior surface of the calcaneus. Its axis passes from the dorsomedial facet of the navicular bone and exits from the lateral plantar facet of the calcaneus. In inversion of the subtalar joint, the calcaneus moves medially, and in eversion the calcaneus moves laterally. The extent of this motion is 6 degrees during level walking in normal foot, and over 9 degrees in flat-footed individuals [4]. The associated motion of the ankle and subtalar joints has been likened to that of a universal joint. The axes of the two joints are intermittently related, allowing compensation between the joints. Failure of this compensatory mechanism produces increased stresses on the adjacent joints and structures, including the tendons. The motion in the hindfoot between talus and calcaneus can be represented by a cone-shaped bundle of discrete axes representing the successive positions of a moving axis [2,3]. This influences the function of the muscles crossing the two joints. The movements of the hindfoot are produced by six muscles that have a stable moment arm during the coupled motion of the two joints [5]. The triceps surae produces an inversion moment arm with the hindfoot in eversion, and the reverse with hindfoot inversion [5], with a switch of joint axis to the opposite site of the line of action of this muscle.

The tibialis posterior muscle has its peak moment arm at the subtalar joint to counteract body weight, and is the main muscle maintaining the arch of the foot. Therefore, it is involved in every movement of the hindfoot, and its tendon can be easily overloaded. From the functional point of view, all the muscles whose tendons run in this region play a role in the stance phase and in the toe off phase. The muscles contract as the forefoot touches the ground. The tibialis posterior and the flexor tendons counteract the pronation of the subtalar joint and the internal rotation of the leg [6] by contracting eccentrically. Any condition decreasing the efficiency of these muscles, such as fatigue, and/or ligaments failure may cause increased pronation with possible overload of all tendons [7]. Immediately after the stance phase, the triceps surae and the tibialis posterior muscles contract and shorten concentrically to push off.

The peroneal tendons work in a different fashion. Peroneus brevis everts the foot, and peroneus longus everts the foot and lowers the first metatarsal. They therefore work in the swing phase of gait, after push-off.

A large os trigonum or a hypertrophic tubercle of the talus can impinge with the tendons of tibialis posterior and/or the long toe flexors, with consequent tendinopathy. This is especially frequent in jumping, but is seen also in hurdling (110, 400 m) and steeplechase, when the foot hits the ground in forced plantar flexion with eccentric contraction of the calf muscles. The ankle then extends dorsally in the stance phase, and returns immediately in plantar flexion in the toe-off phase.

Possible excessive dorsiflexion after impact descending from the hurdle, repeated many times in training and competition, can cause sudden strain around the os trigonum via the bifurcate ligament, but also to the Achilles tendon insertion, and peroneal and tibialis posterior tendons. As described above, excessive overload due to muscle fatigue can increase ground contact time, decrease the buffering action of the myotendinous unit, and consequently place high strains on tendons.

Jumping also overloads the hindfoot. In high jump, the final phase of the run-up and the take-off phase can both damage the hindfoot. The run-up enables the athlete to gain enough speed that can be transformed into vertical translation of his center of gravity. The length of the run-up is usually 9 to 13 steps. Towards the last 25% of the run-up phase, the athlete's position is perpendicular to the axis of the bar, and during the last 3 to 4 steps of acceleration the athlete runs parallel to the bar. In this phase, the athlete's chest must be flexed towards the centre of the curve so that the athlete can gain centrifugal power, and, while the foot of the push-off leg maintains contact with the inner portion of the curve, the foot of the take off leg stays in contact with the lateral border of the curve, increasing supination on ground contact. Errors in the correct execution of this phase can lead to lesions of the hindfoot: If the rhythm of acceleration is limited to the final last two run-up steps instead of the last 3 or 4, there is excessive abrupt pronation of the take-off foot, with possible:

1. Excessive strain to the tibialis posterior tendon at the insertion and along its course.
2. Excessive twisting of the Achilles tendon and strain at the musculotendinous junctions.
3. Strain at the insertion and along the tendon of peroneus longus.

High strains can be reached also during the recovery phase of this abnormal pronation:

1. If excessive lowering of the center of gravity occurs, in the last step the limb is pushed too far forward, resulting in increased plantar flexion of the ankle, with bony impingement of the posterior aspect of the talus.
2. In the take-off phase, the contact time should be as brief as possible; if the foot is excessively pronated, the strains to the tendons can be high.

The number of injuries caused by each of the above mechanisms is high. The diagnostic algorithm for hindfoot pain is shown in Figure 19-1.

Peroneal Tendon Pathology

Peroneal tendon pathology has been neglected: These tendons are often damaged in ankle sprains [8]. The sprain is usually the most evident source of pain, and is addressed first. For this reason, epidemiological data can be biased by a late or failed diagnosis. In a series of 639 consecutive ankle sprains, the peroneal tendons were involved in 83 instances, and the Achilles tendon in 67 instances [9]. With the more diffuse use of ultrasonography and MRI, damaged tendons and/or their sheaths can be easily diagnosed.

The tendons of peroneus longus and brevis run posterior to the lateral malleolus, and are contained by the superior and inferior retinacula within the fibular groove and the lateral surface of the calcaneus. Peroneus brevis inserts in the base of the fifth metatarsal, while peroneus longus, deep to the brevis, inserts medially at the base of the first metatarsal and the first cuneiform. Peroneus brevis everts the foot, and peroneus longus depresses the first metatarsal and everts the foot.

The peroneal tendinopathies can be classified as follows:

Paratendinopathy. This is normally acute, but, if chronic, can stenose the tendons.

Paratendinopathy with intratendinous tendon degeneration. This is normally chronic.

Longitudinal tears are often associated with and/or consequence of an ankle sprain.

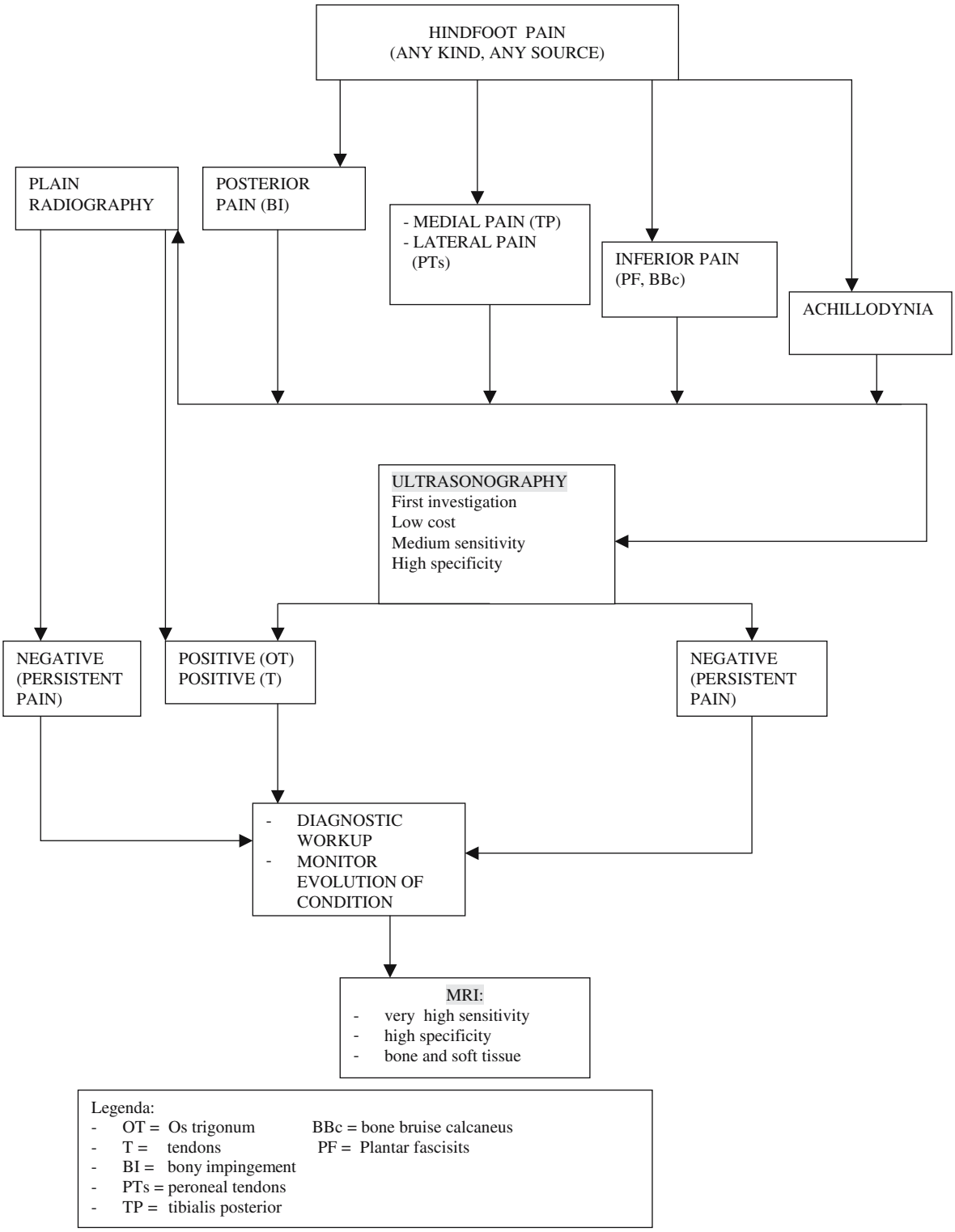

Figure 19-1. Algorithm of diagnosis of hindfoot pain. Ultrasonography is able to diagnose soft tissue derangement, but we suggest that in athletes the investigation must be complemented with MRI, which is able to rule out the bone involvement.

Total rupture

Subluxation/dislocation. These are often associated with parantendinopathy and longitudinal tears [10,11]

Accessory muscle belly can simulate and/or cause tendon pathology.

Paratendinopathy is rare in the general population but relatively frequent in athletes and in dancers as a consequence of an continuous overload from friction against bony surfaces and within the fibrous retinacula. Stenosis can occur in 3 different areas where the pulleys are located:

1. Posteriorly to the lateral malleolus in the peroneal sulcus (peroneus brevis)
2. In the peroneal throclea of the calcaneus where the peroneus longus runs
3. At the inferior edge of the cuboid (peroneus longus)

Furthermore, trauma causing fractures of the lateral malleolus and/or calcaneus, and plating of the fibula may cause or exacerbate friction with inflammation of the tendon sheaths. Chronic inflammation can accompany tendon degeneration, and at that stage a minor ankle injury can cause longitudinal tears of the tendon(s). Pain and tenderness are present behind and below the lateral malleolus, with edema and local swelling. Resisted inversion, adduction and plantar flexion, or active resisted eversion, especially starting from an inverted position, can also cause pain.

Longitudinal tears of both tendons are frequently associated with or caused by a chronic ankle laxity [12]. Pain is exacerbated by local palpation, which reveals an enlarged tendon, and by the above maneuvers. Complete ruptures are rare, and more frequent in rheumatoid patients than in athletes. The diagnosis of longitudinal tears can be achieved by MRI, while sonography can easily reveal the amount of peritendinous swelling.

The true incidence of *subluxation/dislocation* is high when compared to the other pathologies described, and, as stated, can be a primary event. Subluxation or full dislocation occurs when the inverted foot is forcefully dorsiflexed with simultaneous contraction of the peroneal muscles, causing a tear of the superior retinaculum or periosteal avulsion. This can take place when the tip of the ski is caught in the snow, the skier falls forward, the foot is inverted, and the peroneal muscles contract forcefully: The superior retinaculum strips the periosteum from the bone, and the tendons dislocate.

The management of peroneal tendon pathology is varied:

Conservative management of paratendinopathy includes reduction of activity, NSAIDs, orthotics with lateral wedge, and casting to prevent weightbearing. Local steroid injections must be avoided, having little or no benefit, and compromising tendon integrity. These modalities may not be successful if the main cause of the condition is a stenosis. In this instance, surgery with excision of the inflamed and thickened sheaths is mandatory, with careful reconstruction of the retinacula.

In instability, most patients treated conservatively tend to have chronic redislocation of the tendons, while surgical repair has a 75% success rate. A subluxation can be left untreated as long as no secondary tendinopathies occur. In chronic dislocations, many different procedures have been described: bone block procedures, creation of a sling with a strip of the Achilles tendon, transfer of the tendons under the calcaneofibular ligament, fibular grooving, or reefing of the superior peroneal retinaculum.

Medial Retromalleolar Syndrome

The bony-fibrous tunnel behind the medial malleolus contains vascular, nervous and tendinous structures that can be compressed as the tunnel is inextensible. Symptoms from dysfunction of these tightly connected structures are often difficult to differentiate clinically. For this reason, a syndrome resulting from combination of tibialis posterior tendinopathy, plantar fasciitis and tarsal tunnel syndrome has been recently described. Failure of the main static (plantar fascia) and dynamic (posterior tibialis tendon) supports of the longitudinal arch of the foot results in traction injury to the posterior tibial nerve, with tarsal tunnel syndrome: the Heel Pain Triad [13]. Accuracy in clinical assessment and imaging are mandatory to identify the structures involved and to plan management.

Tibialis Posterior Pathology

Tibialis posterior pathologies and valgus flatfoot–pronation deformities are tightly connected. Repeated excessive pronation (for instance in runners) leads to tibialis posterior overuse. On the other hand, tibialis posterior tendinopathy causes eversion of the hindfoot and fall of the medial longitudinal plantar arch resulting in a pronated valgus flatfoot. Consequently, posterior tibialis pathology, including paratendinopathy, chronic degeneration, and rupture, is mainly the result of these dysfunctions.

The portion of the tibialis anterior tendon just beneath flexor retinaculum at the medial malleolus and just distally, four cm proximal its insertion on the navicular, are the least vascularised portions of the tendon [14]. Its pathology is a most important cause of painful acquired flatfoot in adulthood [15,16,17]. Such dysfunction develops progressively with collapse of the medial longitudinal arch, valgus hindfoot and forefoot deformities, and forefoot hypermobility demonstrated by the “too many toes” sign.

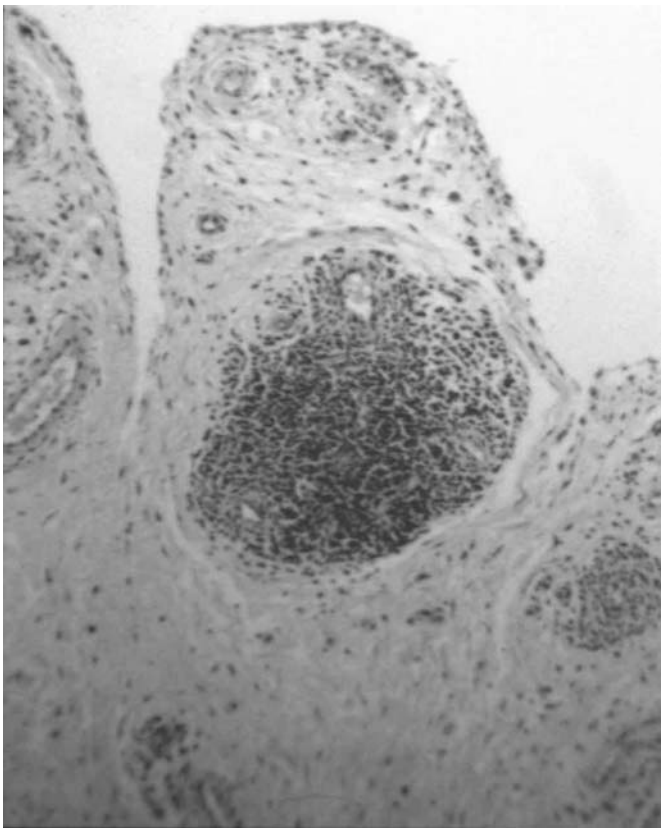

Figure 19-2. Histological appearance of tibialis posterior tendon with villi and follicula. (See color insert.)

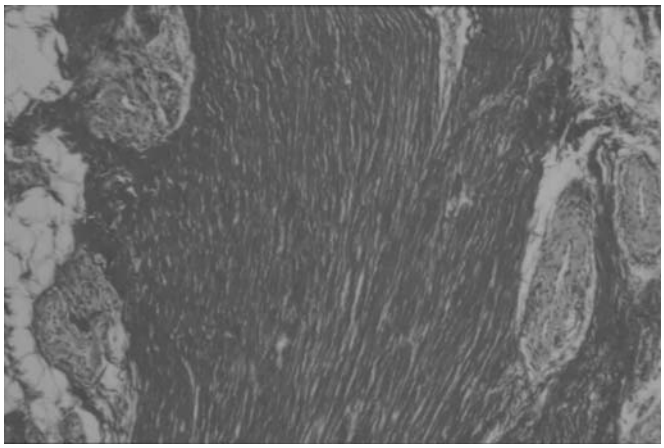

Figure 19-3. The tendinous tissue of tibialis posterior is surrounded by areolar tissue and many newly formed capillaries. (See color insert.)

At surgery, several pathological patterns can be present, such as acute inflammatory paratendinopathy (Figure 19-2, see color insert), and degenerative tendinopathy of the main body of the tendon.

In particular, degeneration leads to a nonspecific response to tissue injury with fibroblast hypercellularity, chondroid metaplasia, mucinous degeneration and neovascularization (Figure 19-3, see color insert) [16]. Collagen structure and orientation are disrupted, and the tendon is predisposed to rupture under physiologic loads (see Figure 19-4A–C, see color insert).

Numerous factors have been proposed to explain the pathophysiology of posterior tibialis tendinopathy:

Mechanical: Ligamentous laxity, articular hypermobility, a shallow retromalleolar groove, a tight flexor retinaculum, navicular bone abnormalities (accessory scaphoid, or prominent navicular tubercle) [18,19]. The action of tendons around the ankle seems to have an important role in the progression of posterior tibialis tendinopathy. As the medial arch falls, and the unopposed action of peroneus brevis pulls the hindfoot in valgus, the actions of the Achilles tendon and tibialis anterior become eccentric and misdirected, amplifying the deformity, while peroneus longus pulls the forefoot in abduction.

There is an area of *hypovascularity* immediately posterior to the medial malleolus. On clinical examination, the examiner looks for insufficiency of this tendon with the patient evaluated standing and seated. With the patient standing, the examiner should ascertain whether a flatfoot, a valgus hindfoot, and abduction of the forefoot are present. A unilateral flatfoot is appreciated with loss of the longitudinal medial arch and fullness in the posteromedial aspect of the ankle. When examining the posterior aspect of the limb, a valgus hindfoot is evident, and more lateral toes can be seen because of abduction of the hindfoot ("too many toes" sign).

Dynamic testing shows whether the patient is able to perform a double or a single toe raise. Subtle signs of tibialis posterior tendinopathy are detectable by asking the patient to repeat the toe raise test. One should check the position of the calcaneus: In the normal foot, it is inverted, whereas in tibialis posterior tendinopathy, the hindfoot remains neutral or valgus. When sitting, edema and tenderness of the posteromedial aspect of the ankle, around the tibialis posterior tendon, or at its insertion on the navicular, are found. Flexion and inversion of the hindfoot against resistance are assessed and compared to the unaffected limb. The range of motion of the ankle, hindfoot, and midfoot should be assessed.

Mobility of the subtalar joint can be markedly limited, and Achilles tendon retraction can be associated with tibialis posterior pathology. In more advanced stages of the condition, with fixed valgus deformity, failure of the deltoid ligament and degeneration of lateral compartment of the ankle may be present. At this time, fixed supination of the forefoot can occur, keeping the foot plantigrade with fixed valgus hindfoot.

Ultrasonography and MRI provide information about the extent of the condition and the degree of tendon

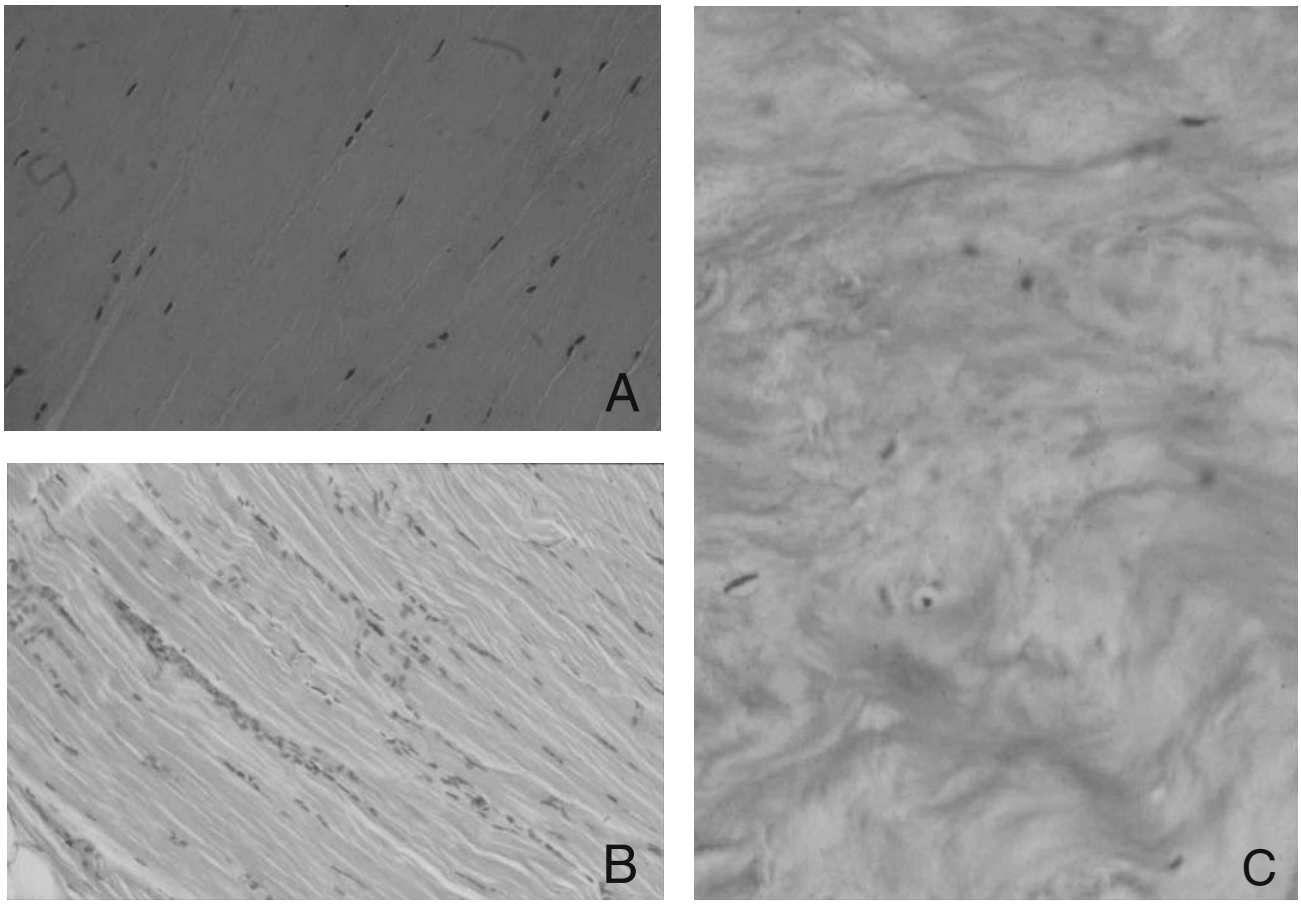

Figure 19-4. Normal tendon with scattererd elongated cells (A), slightly pathologic tendinous tissue (B) with islands of high cellularity and initial disorganization, and highly degenerated tendon with some chondroid cells (C). (See color insert.)

pathology. Ultrasonography identifies paratendinopathy and intratendinous pathology, and, with greater difficulty, partial tears of the posterior tibialis tendon. MRI is more sensitive for tears of the posterior tibialis tendon than clinical or ultrasonographic evaluation. Ultrasonography and MRI are useful to monitor tendon pathology in athletes, while the diagnosis of posterior tibialis tendon tendinopathy in older patients can be formulated on plain radiographs [20].

On anteroposterior radiographs, partial uncovering of the talar head, increase of the talus–first metatarsal angle, and talocalcaneal divergence can be evident. Lateral radiographs may evidence flattening of longitudinal arch, increase of the talus-first metatarsal angle, talocalcaneal divergence, and fall of the talonavicular, naviculocuneiform or tarsometatarsal joints.

Various clinical forms of tibialis posterior tendinopathy are described, and can be considered different stages of the same pathology.

Acute and Chronic Paratendinopathy

The synovium surrounding the tendon can be hypertrophic and edematous, but the main body of the tendon is not, or only minimally, involved (Figure 19-4).

Symptom onset is gradual and relatively aspecific. Signs and symptom of tibialis posterior tendinopathy are present with pain worsened by prolonged weightbearing and walking. Pain is also elicited by retromalleolar palpation, passive eversion and abduction, active inversion,

and adduction. Local swelling is often present, particularly in the posteroinferior portion of the retromalleolar sulcus. Rarely, in chronic paratendinopathy, intratendinous calcifications can be found at ultrasonography or MRI.

Partial and Complete Rupture

Ruptures of the posterior tibialis tendon are often missed. Unlike in the Achilles tendon, ruptures of this tendon are relatively uncommon. Partial tears are more frequently seen in young athletes, and total ruptures are more typical of middle-aged or former athletes [21]. In the zone where the tendon curves around the medial malleolus, its histological structure changes from dense connective tissue to fibrocartilaginous tissue, probably the result of compressive and shear stresses acting around this pulley. Fibrocartilage is avascular and more vulnerable to tensile forces. For these reasons, degenerative changes and ruptures of the tendon are relatively frequent in this region. Diagnosis can be difficult. A history of ankle sprain, especially in high-impact sports, is frequent. The patient has a pronated forefoot and an acquired flatfoot on the affected side. Pain and swelling are generalized on the medial aspect of the ankle, the tibialis posterior is inactive on manual testing, and the patient is usually unable to perform a single-leg heel rise. Clinical signs of tendon failure are absent, but local pain and swelling, pain on resisted eversion and inversion, and an enlarged tibialis posterior tendon can point to the diagnosis.

The management of paratendinopathy of the tibialis posterior tendon follows the classical prescription of rest, NSAIDs, and orthotics, with a longitudinal arch support that prevents eversion. When the main cause of this pathology is friction or stenosis, surgery with excision of the thickened paratenon, longitudinal tenotomy of the tendon and reconstruction of retinaculum is the treatment of choice. For total rupture and avulsion of the tendon, surgery is mandatory.

Plantar Fasciopathy

Plantar fasciopathy affects an aponeurotic fascia, and is in essence an insertional tendinopathy. The plantar fascia starts proximally as a fibrous band of thick dense connective tissue from the anterior calcaneal tuberosity. Progressively wider and thinner distally close to the metatarsal heads, it divides into 5 processes, 1 per toe. The function of the fascia is to maintain with its tension the longitudinal arch, improving the pushing power during running and jumping.

Excessive and prolonged strains on the fascia produce microtears and degeneration at the insertion of the fascia onto the calcaneus. Calcifications, often asymptomatic, can be the result either of periosteum irritation [22] or of bleeding due to microtears [23].

Etiological factors involved in plantar fasciitis include excessive training, excessive pronation, flatfoot, pes cavus, a tight Achilles tendon, calf muscle tightness, training on hard surfaces, and wearing shoes with thin or worn-out soles. The most important risk factor seems to be the range of extension of the ankle, with the risk of plantar fasciitis increasing as ankle dorsiflexion decreases [24]. Other important risk factors are the amount of time spent weightbearing, and being overweight. Patients with plantar fasciitis adjust their gait with reduced force beneath the hindfoot and the forefoot. Furthermore, toe function plays an important role in plantar fasciopathy as a protective factor [25].

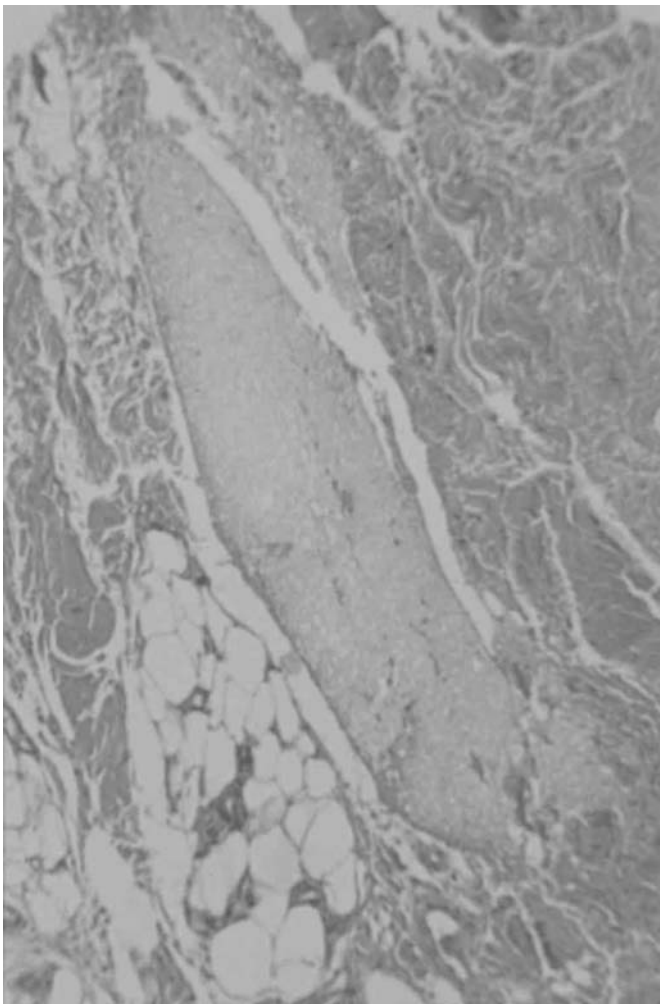

Figure 19-5. Effects of corticosteroids injection: a crystal is surrounded by amorphous and alveolar tissue and the fibrillar organization is no longer recognized. (See color insert.)

From a histological point of view, the fibrous tissue at the insertion on the calcaneum of the plantar fascia is thicker than usual and has lost its well ordered fibrillar organization. At times, granulomatous areas can be found [26]. Histological examination show calcifications of the aponeurosis, cartilaginous metaplasia, fibromatosis [27]. Histopathological findings at surgery suggest that plantar fasciitis is a degenerative condition without inflammation, and therefore not, strictly speaking, a fasciitis. Mixoid degeneration, fragmentation of the plantar fascia, and bone marrow vascular ectasia of the calcaneum were found [28].

Plantar fasciopathy is common in nonathletes and in overweight, middle-aged patients, but is especially found in middle- and long-distance runners, gymnasts, tennis, volleyball, and basketball players, and in triple jumpers. Middle-aged athletes are affected more often than younger athletes.

Patients usually report gradual onset of pain over the plantar aspect of the calcaneum, on the medial aspect of the tuberosity. The onset can be sudden in patients who executed a jump with incorrect contact with the ground. At times, the pain radiated along all the medial plantar aspect. Differential diagnosis includes calcaneal stress fractures, bursitis between the calcaneum and plantar fat pad, fat pad syndrome, tarsal tunnel syndrome, paratendinopathy of the tendons of posterior tibialis, flexor hallucis longus, and flexor digitorum longus, as well as rheumatoid entesitis and trauma.

The management of plantar fasciopathy is usually conservative. Rest and analgesia improve the symptoms, and longitudinal arch supports to decrease the tension on the fascia during activity. Dorsiflexion splint have been proposed to stretch passively the fascia during rest [29]. Local injections of steroids, though often used, should be reevaluated because of their potential to induce fascial rupture in the absence of inflammation (Figure 19.5) Extracorporeal shock wave treatment is still controversial, but can be used in selected patients [28].Taping may be useful in the first few days after and acute lesion and when athlete enter advanced rehabilitation with running and sport activity.

Surgery with partial release of the medial insertion can be undertaken if conservative management is unsuccessful, but recovery can be long, and full success is achieved in only about 70% of patients.

Flexor Hallucis Longus Syndrome

Flexor hallucis longus tendinopathy is frequent in dancers, but disorders of this tendon are often overlooked in other individuals. The tendon of flexor hallucis longus inserts in the distal phalanx of the hallux. Along its course, 3 zones of stenosis are present:

1. Behind the medial malleolus the tendon runs between the talus and the medial malleolus, in the bony/fibrous tunnel that contains the neurovascular pedicle, the tibialis posterior, and flexor digitorum tendons. This tunnel acts as a pulley, and at this level the tendon may be compressed and thus its synovium irritated. The presence of an accessory tendon or muscle belly has been described as a cause of compression in the tunnel [30]. Furthermore, an enlarged os trigonum, calcaneal fractures, and soft tissue scars can entrap the tendon of flexor hallucis longus at this level [31].
2. At Henry's node, where, on the plantar aspect of the first metatarsal, the tendon of flexor digitorum longus passes close to the tendon of flexor hallucis longus.
3. The third site is between the two sesamoid bones at the plantar side of the head of the first metatarsal [32].

In dancers, the *en pointe* position stresses the tendon of flexor hallucis longus as a dynamic stabilizer of ankle and foot. Furthermore, in dance and in other sports, hyperpronation strains the tendons at the retinaculum, leading to inflammation and predisposing it to intratendinous degeneration.

The anatomopathological features are similar to other tendinopathies. The synovium is thicker than normal (Figure 19-2) and effusion and inflammation can be present. The tendon is thinner, and microtears are frequents as result of chronic degeneration. Pseudocysts or calcified nodules and fibrosis can be seen. Microscopically, normal appearance, aspecific tenosynovitis and tendinosis can all be seen, with oedema, fibre disorganization, mucoidocystic degeneration, scarring, and nodules.

Clinical features include pain and discomfort in the medial retromalleolar region of fibro-osseous tunnel elicited by flexion of the toes. Sometimes, hyperesthesia or crepitation are present. Fullness between the Achilles tendon and the tibia as result of edema and inflammation of the synovium within the tunnel can also be present. There can be stiffness of the hallux with limited dorsiflexion at the metatarsophalangeal (MTP) joint when the ankle is extended. Rarely, nodules can be palpated, or a click can be felt as a nodule in the tendon passes under the retinaculum.

Dislocation of the tendon of flexor hallucis longus has been described. In this instance, together with the above mentioned features, a snap will be triggered by maximal ankle dorsiflexion combined with plantar flexion of hallux at the metatarsofalangeal joint. MRI is the imaging modality of choice. Patterns of paratendinopathy, images of pseudocysts, degeneration, tears or microtears of tendon as well as an abnormal position (i.e. in case of dislocation) are detectable.

Early recognition of the tendinopathy is important for

a successful treatment. In the acute phase, rest, analgesia and avoidance of extreme plantar flexion can be helpful. Surgical management is controversial. Some authors [33] prefer conservative management, believing that scar tissue caused by surgery will lead to a persistent pain. When conservative treatment has failed, surgery must be undertaken to remove the cause of stenosis, free the tendon, and remove degenerated intratendinoous areas.

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20
Achilles Tendon Rupture

Deiary Kader, Mario Mosconi, Francesco Benazzo, and Nicola Maffulli

Introduction

The incidence of Achilles tendon rupture in developed countries has been on the increase over the past 2 decades [1]. Although most Achilles tendon ruptures (44% to 83%) occur during sporting activities, intrinsic structural, biochemical, and biomechanical changes related to ageing may play a significant role [2].

Achilles tendon rupture is more common in males, with a male-to-female ratio of 1.7:1 to 30:1, possibly reflecting the greater prevalence of male sports participation, or their susceptibility to injury. Typically, an acute rupture of the Achilles tendon occurs in male professionals or white collar workers in their third or fourth decade playing sports occasionally (weekend warriors).

History

Hippocrates, in the first recorded description of this injury, stated that "this tendon, if bruised or cut, causes the most acute fevers, induces choking, deranges the mind and at length brings death." Ambroise Paré, in 1575, recommended that a ruptured Achilles tendon be strapped with bandages dipped in wine and spices, but advised that the result was dubious [3]. Operative repair of a ruptured Achilles tendon was advocated by another Frenchman, Polaillon, in 1888 [3], although an Arabian physician performed such procedures in the 10th century AD. In the 12th century, an Italian surgeon, Guglielmo di Faliceto, believed that nature was unable to unite divided tendons, and that operative treatment was necessary.

Anatomy and Histology

The gastrocnemius merges with the soleus to form the Achilles tendon. This is supplemented medially by plantaris in 93% of the population. The Achilles tendon has a round upper part and relatively flat distal 4 cm. The fibers of the Achilles tendon spiral through 90 degrees along its course to help tendon elongation, elastic recoil, and release of stored energy during locomotion [4].

Tenocytes and tenoblasts comprise about 90% to 95% of the cellular elements of the tendon. Collagen and elastin fibers account for 70% and 2% of the dry weight of a tendon, respectively, and form a major part of the extracellular matrix. Elastin can undergo up to 200% strain before failure [5].

The collagen fibers are tightly packed in parallel bundles containing blood and lymphatic vessels, and nerves [6,7]. Type I collagen is the commonest, being 95% of tendon collagen [8]. However, ruptured Achilles tendons contain a substantial proportion of Type III collagen [9], which is less resistant to tensile forces.

The tendon is formed by grouped fascicles surrounded by endotenon, and is enveloped by a well-defined layer of connective tissue, the epitenon, whose innermost layer is in direct contact with the endotenon. The epitenon, in turn, is surrounded by the paratenon, with a thin layer of fluid in between to allow tendon movement with reduced friction.

The paratenon consists of 2 layers: a deeper layer, surrounding and in direct contact with the epitenon; and a superficial layer, the peritenon, which is connected with the underlying layer via the mesotenon. The paratenon is externally in contact with the fascia cruris covering the tendon posteriorly [8,10].

Aging significantly decreases tendon glycosaminoglycans and increases collagen concentration [11]. Acute exercise increases type I collagen formation in peritendinous tissue [12].

The Achilles tendon derives its sensory nerve supply from the nerves of the attaching muscles and cutaneous nerves, in particular the sural nerve [13], and receives its blood supply proximally at the musculotendinous junction, along its length from the surrounding connective tissue, and distally at the bone-tendon junction [14]. The predominant site of Achilles tendon rupture is 2 to 6 cm

proximal to the tendon insertion. Although this has been attributed to poor vascularity in the mid-portion, Astrom et al. [15], using laser Doppler flowmetry, showed that there is even blood flow throughout the Achilles tendon, apart from the distal insertion. They also showed that blood flow was higher in women comparing to control and lower with increasing age. In another study, the posterodistal and the middle part of the Achilles tendon showed poor vascularization [16].

Blood flow in the Achilles tendon increases fourfold with exercise 5 cm proximal to the insertion, while it increases only 2.5 times when measured 2 cm proximal to the Achilles tendon insertion [17].

Tendon Biomechanics

Tendons have almost ideal mechanical properties for transmission of force from muscle to bone. Actin and myosin are present in tenocytes [18]. Tendons are stiff and resilient, with high tensile strength. They can stretch up to 4% before damage [19]. Subcutaneous tears are more frequent in the Achilles tendon than in any other tendons in the human body. Achilles tendons in males have higher maximum rupture force and stiffness with a larger cross-sectional area than in females, while younger tendons have significantly higher tensile rupture stress and lower stiffness [20].

The indirect estimation of peak load on the Achilles tendon, normalized to subject body weight, is 6.1 to 8.2 times the body weight during running, with a tensile force of >3 kN [21]. The loading of the Achilles tendon reached up to 9 kN during running (12.5 times the body weight), 2.6 kN during slow walking, and <1 kN during cycling [22]. The peak Achilles tendon force and mechanical work by the calf muscles measured by Fukashiro et al. was 2233 N and 34 J in the squat jump, 1895 N and 27 J in the countermovement jump, and 3786 N and 51 J when hopping [23].

Microscopic interruptions in the tendinous substance occur during physiological activity, but fibers remodel, and new collagen is continuously formed. A tendon loses its wavy configuration when stretched >2%. As collagen fibers deform, they respond linearly to increasing tendon loads [19,24,25]. The normal wavy appearance of the tendon is regained if the strain placed on the tendon remains at <4%. If the tendon is lengthened >3% to 4% of its normal length, it starts to disrupt. At strain levels greater than 8%, macroscopic rupture will occur [26,27].

Etiology and Pathology

The etiology of Achilles tendon rupture has been thoroughly researched, but still remains unclear [28]. Achilles tendon rupture has been attributed to many factors such as poor tendon vascularity, degeneration, gastrocnemius-soleus dysfunction, a suboptimally conditioned musculotendinous unit, age, gender, changes in training pattern, poor technique, previous injuries, and footwear [29–32]. It has also been associated with a multitude of conditions, such as inflammatory and autoimmune conditions, hyperuricemia, genetically determined collagen abnormalities [33], infectious diseases, neurological conditions [34], hyperthyroidism, renal insufficiency, and arteriosclerosis [35].

Degenerative Theory

The events leading to a rupture are unclear [36,37]. Normal tendons would not rupture when subjected to large strains [38]. Arner et al. [39] first reported degenerative changes in all their 74 patients with Achilles tendon rupture, and hypothesized that these changes were primary abnormalities present before the rupture. However, nearly two-thirds of the specimens were obtained >2 days post rupture. Davidsson and Salo [40] reported marked degenerative changes in 2 Achilles tendon rupture patients operated on the day of injury. The changes should therefore be regarded as having developed prior to the rupture [41]. In our own series, all tendons operated within 24 hours from the injury showed marked degenerative changes and collagen disruption [42,43] (see Figure 20-1). Several authors detected degenerative intratendinous alterations in the spontaneously ruptured tendons from all sites studied. Most of these abnormalities had no etiological explanation [44]. Probably, alterations in blood flow with subsequent hypoxia and impaired metabolism were factors in the development of the degenerative changes observed [45].

Alternating exercise with inactivity could produce the degenerative changes seen in tendons. Sport places additional stress on the Achilles tendon, leading to accumu-

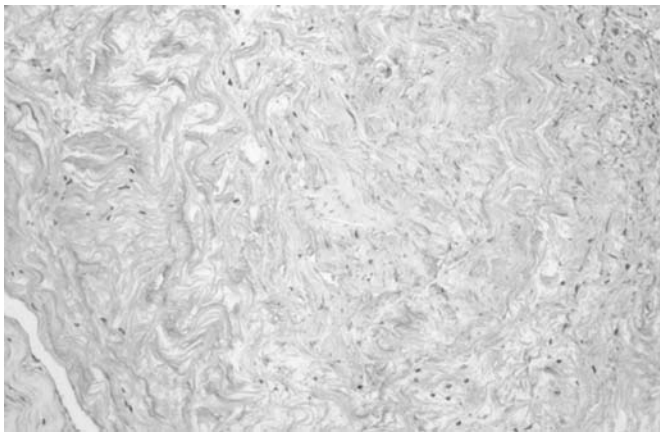

FIGURE 20-1. Histology slide of a ruptured Achilles tendon. Note the disorganized appearance, with loss of the normal wavy configuration of the tendon and marked hypercellularity.

lation of microtrauma, which, although below the threshold for frank rupture, could lead to secondary intratendinous degenerative changes [46].

Kannus and Jozsa evaluated biopsy specimens of patients with spontaneous Achilles tendon ruptures harvested at the time of repair. Only one-third of control tendons had similar changes, but significantly less frequently [45]. They also noted that only relatively small proportion of the patients had symptoms prior to the rupture. They suggested that there are clear indications that, at least in urban populations, degenerative changes are common in the tendons of people who are older than 35 years, and that these changes can be associated with spontaneous rupture [45].

In our center, of the 176 Achilles tendon ruptures treated from January 1990 to December 1995, we found that only 9 patients (5%) had had previous symptoms [47]. Failure of the cellular matrix may also lead to intratendinous degeneration. Jozsa et al. observed fibronectin on the torn surfaces of ruptured Achilles tendons. Fibronectin is normally located in basement membranes, is present in a soluble form in plasma, and binds more readily to denatured collagen than to normal collagen, indicating preexisting collagen denaturation [48–50].

We have recently demonstrated that tenocytes from ruptured and tendinopathic tendons show increased production of Type III collagen, which disturbs the tissue architecture, and makes the tissue less resistant to tensile forces [47].

The Mechanical Theory

Damage to the tendon can occur even though it is stressed within the physiologic threshold when the frequent cumulative microtrauma applied do not leave enough time for repair [51].

McMaster [52] thought that a healthy tendon would not rupture, even when subjected to severe strain. However, Barfred [53] demonstrated that complete ruptures can occur in a healthy tendon, the greatest risk being present when the tendon was obliquely loaded at a short initial length with maximum muscle contraction. Such factors are probably all present in movements occurring in many sports, which require rapid push-off. A healthy tendon may, therefore, rupture following a violent muscular strain.

Inglis and Sculco [29] suggested that a malfunction in the inhibitory mechanism that prevents excessive or uncoordinated muscle contractions could cause a rupture of an otherwise normal tendon. Athletes who return to training too quickly after a period of inactivity seem to be at greater risk of a rupture due to this mechanism. The risk of rupture of the Achilles tendon is further increased if an oblique stress is applied during inversion or eversion of the subtalar joint.

In a study of 109 runners, Clement showed that Achilles tendon injury may result from structural or dynamic disturbances in normal lower leg mechanics, such as overtraining, functional overpronation, and gastrocnemius/soleus insufficiency. They also speculated that repeated microtrauma produced by the eccentric loading of fatigued muscle may play an important role in tendon injury [54]. Complete rupture is the consequence of multiple microruptures, which lead to failure of the tendon after reaching a critical point [55].

Drug-Related Tendon Rupture

Anabolic steroids and fluoroquinolones have been related to Achilles tendon rupture. Both drugs cause dysplasia of collagen fibrils, which decreases tendon tensile strength.

Systemic and local corticosteroids have been widely implicated in tendon rupture [56,57]. However, studies on the patella tendon show that normal tendon is not damaged by intratendinous injection of steroids [58]. However, most of the available evidence suggests that intratendinous or peritendinous injection of corticosteroids into an injured tendon may precipitate a rupture [59,60].

The etiological role of corticosteroids in Achilles tendon rupture has not been fully clarified. However, available evidence discourages from prolonged oral administration and repeated peritendinous administration of corticosteroids. The anti-inflammatory and analgesic properties of corticosteroids may mask the symptoms of tendon damage [61], inducing individuals to maintain their high activity levels even when the tendon is damaged. Corticosteroids interfere with healing, and intratendinous injection of corticosteroids results in weakening of the tendon for up to 14 days postinjection. The disruption is directly related to collagen necrosis, and restoration of tendon strength is attributable to the formation of a cellular amorphous mass of collagen. For these reasons, vigorous activity should be avoided for at least 2 weeks following injection of corticosteroids in the vicinity of a tendon [59].

Fluoroquinolone (4-Quinolone) antibiotics such as ciprofloxacin have recently been implicated in the etiology of tendon rupture. In France between 1985 and 1992, 100 patients taking fluoroquinolones suffered tendon disorders, including 31 ruptures [62]. Many of them had also received corticosteroids, making it difficult to solely implicate the fluoroquinolones. Szarfman et al. [63] reported animal studies with fluoroquinolone doses close to those administered to humans, and showed disruption of the extracellular matrix of cartilage, chondrocyte necrosis, and depletion of collagen. The abnormalities seen in animals might also occur in humans. These authors recommended updating the labeling on fluoro-

quinolone packaging to include a warning about the possibility of tendon rupture. Recently, laboratory evidence for the direct deleterious effects of fluoroquinolones on tenocytes has been produced [64].

Hyperthermia and Tendon Rupture

Up to 10% of the elastic energy stored in tendons may be released as heat [65]. Wilson and Goodship evaluated *in vivo* the temperatures generated within equine superficial digital flexor tendons during exercise [66]. A peak temperature of 45 degrees C, at which tenocytes can be damaged, was measured within the core of the tendon after just 7 minutes of trotting [67]. Exercise-induced hyperthermia may therefore contribute to tendon degeneration. As good blood supply to a tissue should prevent overheating, tissues such as the Achilles tendon, with relatively avascular areas, may be more susceptible to the effects of hyperthermia.

Mechanism of Rupture

Arner and Lindholm [68] classified the mechanism of Achilles tendon rupture in 92 patients into 3 main categories:

1. 53% of the ruptures occur during weightbearing, with the forefoot pushing off with the knee in extension. This movement is seen in sprint starts, and in jumping sports such as basketball. This would explain the prevalence of left Achilles tendon rupture in right-handed people.
2. 17% of ruptures occur following sudden unexpected dorsiflexion of the ankle, such as slipping into a hole, or falling downstairs.
3. In 10% of their patients, the tendon was ruptured due to violent dorsiflexion of a plantar flexed foot, such as what may occur after falling from a height. In the rest of their patients, they could not identify the exact mechanism of injury.

Presentation and Diagnosis

Detailed history and thorough physical exam are critical in the diagnosis of Achilles tendon rupture. Although the diagnosis seems straightforward, 20% to 25% of Achilles tendon ruptures are missed by the first examining doctor [69]. There are a number of diagnostic signs and tests—both clinical and at imaging—that the examiner may use to aid diagnosis. In general, clinical diagnosis is sufficient for acute ruptures of the Achilles tendon. Long-standing ruptures may be harder to diagnose due to associated tissue swelling. Real-time, high-resolution ultrasonography and magnetic resonance imaging provide an adjunct to clinical diagnosis, and they are more sensitive and less invasive than soft tissue radiography or xeroradiography.

Patients with ruptured Achilles tendon typically give a history of sudden pain in the affected leg, often reporting that, at the time of injury, they thought that they had been struck by an object or kicked in the posterior aspect of the lower leg. Some patients report an audible snap. They are often unable to bear weight, and notice weakness or stiffness of the affected ankle. However, they may be still able to plantar flex using the flexor hallucis longus, flexor digitorum longus, tibialis posterior, and peroneal tendons. Patients with chronically ruptured Achilles tendons often tend to recall only very minor or perhaps no trauma, and first noticing the injury as an inability to complete everyday tasks such as climbing stairs.

Examination may reveal diffuse edema and bruising, and, unless the swelling is severe, a palpable gap may be felt along the course of the tendon. The site of rupture is usually 2 to 6 cm proximal to the insertion of the tendon [70].

Inspection and palpation should be followed by other tests to confirm the diagnosis. Although the Simmonds test is usually reliable, it can be equivocal. In such cases, O'Brien and Copeland tests can be performed. Also, the patient could simply be asked to perform heel rises.

Simmonds or Thompson Calf Squeeze Test

With the patient prone on the examination couch and the ankles clear of the couch, the examiner squeezes the fleshy part of the calf. Squeezing the calf deforms the soleus muscle, causing the overlying Achilles tendon to bow away from the tibia, producing plantar flexion of the ankle if the tendon is intact [71]. The affected leg should always be compared with the opposite leg [72]. A false positive may occur in the presence of an intact plantaris tendon, although this has not been scientifically proven.

Matles Test

Prone on the examination couch, patients are asked to actively flex their knees to 90°. During this movement, if the foot on the affected side falls into neutral or dorsiflexion, an Achilles tendon rupture can be diagnosed [73] (see Figure 20-2).

O'Brien Test

A hypodermic 25-gauge needle is inserted through the skin of the calf, just medial to the midline and 10 cm proximal to the superior border of the calcaneus. The needle is inserted until its tip is just within the substance of the tendon. The ankle is then alternately plantarflexed and dorsiflexed. If, on dorsiflexion, the needle points distally, the tendon is presumed to be intact in the portion distal to the needle. If the needle points proximally or remains relatively still when the ankle is dorsiflexed, there is presumed to be a loss of continuity between the needle and the site of tendon insertion [69].

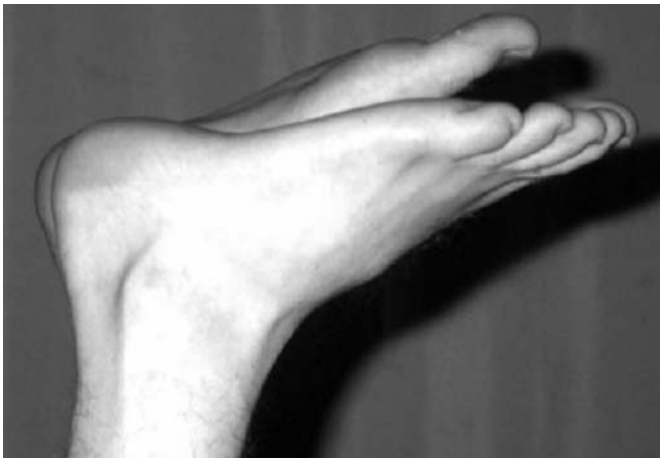

FIGURE 20-2. Matles test. The plantar aspect of the foot ipsilateral to the ruptured tendon lies flatter as compared to the normal side.

Copeland Test

The patient should lie prone with the knee flexed to 90°. A sphygmomanometer cuff is wrapped around the bulk of the calf of the affected leg. The cuff is inflated to 100 mmHg with the foot in plantar flexion. The foot is then dorsiflexed. If the pressure rises to approximately 140 mmHg, the musculotendinous unit is presumed to be intact. If, however, the pressure remains at around 100 mmHg, an Achilles tendon rupture may be diagnosed. The opposite leg may be used as a control for comparison purposes [74].

Plain Radiography

Von Saar in 1914 and Karger in 1939 reported that radiographs provide useful information about injured Achilles tendons [75,76]. Although plain soft tissue radiography is no longer the imaging modality of choice in tendon disorders, it still has a role in diagnosing associated or incidental bony abnormalities.

Lateral radiographs of the ankle have been used to diagnose an Achilles tendon rupture. When the Achilles tendon is ruptured, Kager's triangle (the fat-filled space triangularly between the anterior to the Achilles tendon, the posterior aspect of the tibia, and the superior aspect of the calcaneum) loses its regular configuration. Toygar sign [77] involves measuring the angle of the posterior skin surface curve seen on plain radiographs, as the ends of the tendon are displaced anteriorly following a complete tear. The posterior aspect of Kager's triangle then approaches the anterior aspect, and the triangle decreases or disappears. An angle of 130 to 150° would indicate Achilles tendon rupture. Arner et al. [78] found that deformation of the contours of the distal segment of the tendon resulting from loss of tone were the radiographic changes most likely to be associated with Achilles tendon rupture.

Ultrasonography

Although ultrasonography of the Achilles tendon is operator dependent, it is a primary imaging method [79]. Linear ultrasonography of the Achilles tendon produces a dynamic and panoramic image of the tendon, the appearance of which varies with the type of transducer used and the angle of the ultrasound beam with respect to the tendon. High- frequency probes of 7.5–10 mHz provide the best resolution, but have a short focusing distance [80]. The Achilles tendon is composed of longitudinally arranged collagen bundles, which reflect the ultrasound beam. The probe should be held at right angles to the tendon to ensure that an optimal amount of ultrasonic energy is returned to the transducer, avoiding artefacts. Linear-array transducers are therefore better suited than sector-type transducers, which produce excess obliquity of the ultrasound beam at the edges. It may also be necessary to use a synthetic gel spacer or stand-off pad, increasing the definition of the surface echoes and allowing a suitable support [81].

A normal Achilles tendon appears as a hypoechogenic, ribbonlike image contained within 2 hyperechogenic bands. Tendon fascicles appear as alternate hypo- and hyperechogenic bands separated when the tendon is relaxed, and more compact when strained [81]. Rupture of the Achilles tendon is seen on ultrasonography scans as an acoustic vacuum with thick, irregular edges [81]. Ultrasonography can be used to assess the tendon structure following operative repair.

Magnetic Resonance Imaging

The normal Achilles tendon is seen as an area of low signal intensity on all pulse sequences used. The tendon is well delineated by the high signal intensity of the fat pad of Kager's triangle. Any increase in intratendinous signal intensity should be regarded as abnormal [82]. Axial and sagittal plane T1 and T2 weighted images should be used to evaluate suspected Achilles tendon ruptures. In T1 weighted images, complete ruptures of the Achilles tendon are identified as disruptions of the signal within the tendon. In T2 weighted images, the rupture is demonstrated as a generalized increase in signal intensity, and the edema and hemorrhage at the site of rupture are seen as an area of high signal intensity.

Management of Acute Achilles Tendon Rupture

The management of an acutely ruptured Achilles tendon still largely depends on the preference of the surgeon and the patient. Nonoperative management regained favor

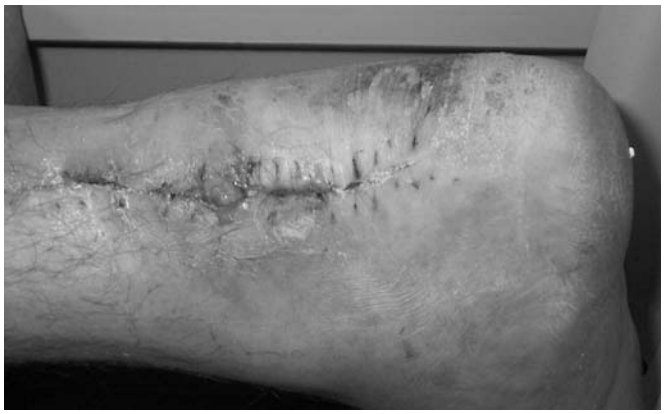

FIGURE 20-3. Superficial infection following open Achilles tendon repair.

during the 1970s. Operation has been the method of choice in the last 3 decades in athletes and young people, and in delayed ruptures. Acute ruptures in nonathletes may also be treated conservatively [83].

Nonoperative Management

Several authors oppose operative repair, citing the high complication rate as the main disadvantage. More recent studies on larger populations reported a much lower complication rate [29,84]. These complications include skin necrosis, wound infection (see Figure 20-3), sural neuromas, adhesions of the scar to the skin, and the usual anesthesia risks. Problems with wound healing remain the most common and most difficult to manage, given the degree of a vascularization around the Achilles tendon. Members of the conservative camp point out that the options for soft tissue coverage over the Achilles tendon are limited. Unfortunately, skin grafts will not adhere to an exposed tendon, and local flaps may result in an unsightly donor site and an unacceptable scar. Therefore, these large defects often require a microvascular free flap.

Despite the continuous improvement in operative technique and experience, wound problems can not be fully eliminated when open repair is used, as the most commonly used longitudinal incision passes through poorly vascularized skin [85]. Aldam [86] used a transverse incision just distal to the gap in the tendon, with just one case of wound breakdown in 41 patients.

Supervised Neglect

Elderly patients with chronic Achilles tendon rupture who are biologically above 70 years of age can be treated with physiotherapy alone. Usually, these patients complain of weakness in plantar flexion and of a strange gait. They often adapt well to their disability.

Immobilization

A most commonly used form of nonsurgical management is by plaster cast immobilization, usually for a period of 6 to 10 weeks [87]. Good clinical outcomes following cast immobilization are reported, with comparable results to operative management [88,89]. A *Lancet* editorial stated: ". . . in view of the excellent results obtainable by conservative treatment, it is doubtful whether surgical repair in closed rupture of the Achilles tendon can be justified [90]."

The paratenon should not be unduly injured by surgical repair of the tendon, as it is important to maintain a smooth gliding surface and to provide vascular supply to the damaged tendon. Stripping of the paratenon, which can remain intact following a rupture, reduces the amount of reactive tissue produced later at the site of injury.

Although function following nonoperative repair is generally good, the high incidence of rerupture is considered unacceptable. In 1972, Lea and Smith reported on 66 patients who underwent 8 weeks of below-the-knee cast immobilization with the foot in gravity equinus followed by a 2.5-cm heel lift for 4 weeks after cast removal. They had seven reruptures (13%) in 55 spontaneously ruptured Achilles tendons [88].

Persson and Wredmark reported on 20 patients managed nonoperatively. After removal of the plaster, 7 patients had a rerupture (35%), 4 of them were operated on, while 2 others sustained a deep vein thrombosis with an associated pulmonary embolus in one case. At follow-up, between 6 and 29 months after the rupture, 16 patients had no complaints, and the remaining 4 had only minor problems. Seven patients, not necessarily those whose tendons had reruptured, were not satisfied with the result [91].

Recently, based on the work on functional postoperative bracing, McComis et al. [92] treated 15 patients who had sustained a rupture of the Achilles tendon nonoperatively with functional bracing. They achieved good functional results. In selected cases, functional bracing may be a viable alternative to operative intervention or use of a plaster cast for the treatment of acute ruptures of the Achilles tendon.

Physiological Effects of Immobilization Following Achilles Tendon Rupture

Immobilization results in profound alteration of muscle morphology and physiology [93]. The soleus muscle is particularly susceptible to immobilization, while the gastrocnemius, being a biarticular muscle, is able to move when a short-leg cast is used, and is thus less affected. The human soleus contains a high proportion of Type I muscle fibers, particularly susceptible to atrophy if immobilized, as they are responsible for postural tone, and are contin-

ually activated while standing [94]. Problems due to immobilization occur after open operative as well as nonoperative management, but not to the same extent. Häggmark et al. [95] studied 15 operatively and 8 nonoperatively treated subcutaneous Achilles tendon ruptures, and found a significant decrease in calf circumference in the nonoperatively treated group, while the operatively treated group showed no significant difference when compared to the uninjured contralateral tendon.

Patients with open operative repairs spend less time in plaster, and on the whole are often more serious athletes who will comply well with postoperative management. The lack of tension on the immobilized musculotendinous unit is a major factor in the development of calf atrophy. If optimal results are required from a repair of a ruptured Achilles tendon, the repair should be put under as much tension as possible as early as possible, and the casts should be changed regularly, decreasing the angle of plantar flexion at each change.

A viable alternative is to immobilize the patient with the foot and ankle plantigrade [96]. This minimizes plaster changes, and the discomfort at the time of plaster changes, when the ankle must be progressively dorsiflexed. It requires a sufficiently strong repair, which can be subjected to early tensile stresses.

Open Operative Management

Surgical Treatment

In the past 2 decades, surgery has been the treatment of choice for Achilles tendon ruptures in young, fit individuals. Advances in surgical techniques and new postoperative rehabilitation protocols have encouraged many surgeons to favor direct tendon repair [35]. Furthermore, surgical repair decreases rerupture rate from 13% to 20% to 1% to 4%, increases tendon strength, and causes less calf muscle atrophy, also helping higher numbers of athletes returning to preinjury physical activities.

Surgical Technique

Different operative techniques can be employed to repair ruptured Achilles tendons, ranging from simple end-to-end suturing by Bunnell- or Kessler-type sutures, to more complex repairs using fascial reinforcement or tendon grafts, artificial tendon implants using materials such as absorbable polymer–carbon fiber composites [98], Marlex mesh, and collagen tendon prostheses [99]. Primary augmentation of the repair [100] with the plantaris tendon [101], the peroneus brevis tendon, a single central or 2 (one medial, one lateral) gastrocnemius fascial turndown flap, was also proposed. However, there is no evidence that, in acute Achilles tendon ruptures, this is better than a nonaugmented end-to-end repair [102]. We prefer to use augmentation in delayed repairs and in the management of reruptures.

Open Primary Acute Achilles Tendon Repair

The patient is placed in the prone position, head 20° down with both feet dangling from the end of the table. An 8- to 10-cm longitudinal incision is made just medial to the medial border of the tendon, centered on the palpable gap. The subcutaneous fat is dissected sharply with no undermining or crushing of the skin edges.

The paratenon is cut longitudinally in the midline for the length of the skin incision. The paratenon is often edematous, and the ruptured ends classically have a mop-end or a horsetail appearance (see Figure 20-4). After juxtaposing the ends, the tendon is sewn together with strong absorbable suture, such as number 2 Vicryl using the Kessler method. Prior to tying the suture ends, the ankle is plantarflexed by an assistant to aid apposition of the tendon ends. A running circumferential suture with finer absorbable suture material is used to further strengthen the repair site. After closing the paratenon with fine Vicryl, the subcutaneous tissues are juxtaapproximated with a deep fat continuous suture. The skin is closed with Steri-Strips to minimize tension. The leg is then immobilized in a below-knee cast with the ankle in physiological equinus. After the operation, the limb is elevated, and weightbearing is started on the day of operation as tolerated with crutches with supervision by a physiotherapist. Patients are advised on discharge to keep the leg elevated as long as possible.

The cast is removed at 2 weeks, when the ankle is placed plantigrade with an anterior removable synthetic cast slab is applied to prevent extension beyond neutral. The patient is encouraged to bear weight as actively as possible and to perform ankle plantar flexion as much as possible.

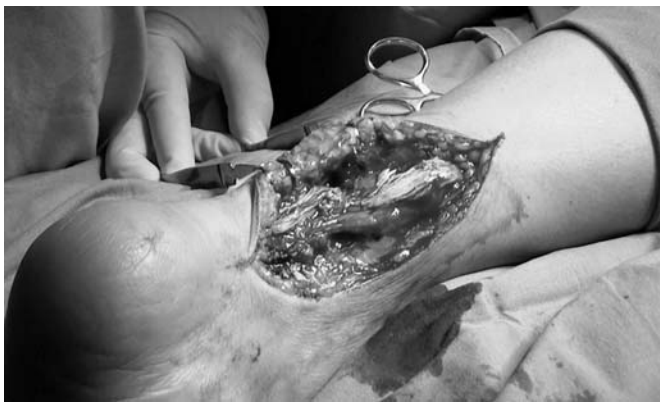

FIGURE 20-4. Classical horsetail appearance of an Achilles tendon rupture.

Percutaneous Repair

In 1977, Ma and Griffith [103] described a technique for percutaneous repair as a compromise between open operative methods and conservative management. The technique involves producing 6 small stab incisions along the medial and lateral borders of the tendon, then passing a suture through the tendon using these incisions. Ma and Griffiths reported 18 patients treated by this technique. There were only 2 minor, noninfectious skin complications and no reruptures. FitzGibbons reported good results in 14 patients who had percutaneous repair, with one sural nerve injury [104].

In our center, Rowley and Scotland [105] described 24 patients with rupture of the Achilles tendon, 14 treated by casting in equinus position alone, and 10 treated by percutaneous repair. One patient with percutaneous repair suffered entrapment of the sural nerve, but no other complications were encountered. Patients in the sutured group were more likely to return to near normal plantar flexion strength, and they also returned to activity sooner than the group treated by cast alone. Other authors report a much lower success rate with this technique. Klein et al. [106] reported sural nerve entrapment in 13% of 38 patients. Hockenbury and Johns [107] compared the *in vitro* percutaneous Achilles tendon repair to open Achilles tendon repair using a transverse tenotomy of the Achilles tendon in 10 fresh-frozen, below-the-knee cadaver specimens. The specimens were divided into 2 groups of 5 specimens each, one receiving open Achilles repair using a Bunnell suture technique, the other undergoing percutaneous repair using Ma and Griffith's technique. The tendons undergoing open repair were able to resist almost twice the amount of ankle dorsiflexion compared to those undergoing percutaneous repair before a 10-mm gap in the repaired tendon appeared (27.6 degrees versus 14.4 degrees, $p < 0.05$). Entrapment of the sural nerve occurred in 3 of 5 specimens undergoing percutaneous repair. The tendon stumps sutured using the percutaneous technique were malaligned in 4 of 5 specimens. Based on this study, this technique of percutaneous repair of Achilles tendon ruptures provides approximately 50% of the initial strength afforded by open repair, and places the sural nerve at risk for injury. Percutaneously repaired Achilles tendons are less thick than those repaired by open procedures, and some patient may prefer the better cosmesis that this may afford [108]. Overall, most studies demonstrate a higher rerupture rate associated with percutaneous repair as compared with open operative repair [108]. Also, worryingly high rates of transfixion of the sural nerve have been reported [105,107], with persistent paresthesiae and the necessity of formal exploration to remove the suture and free the nerve [106].

Recently, Webb and Bannister described a new percutaneous repair technique. The repair is carried out under local anesthesia using 3 midline, transverse, 2.5-cm incisions over the posterior aspect of the tendon (Figure 20-5). They reported no injuries to the sural nerve or late reruptures in 27 patients who had a percutaneous repair at a median interval of 35 months after the injury [109].

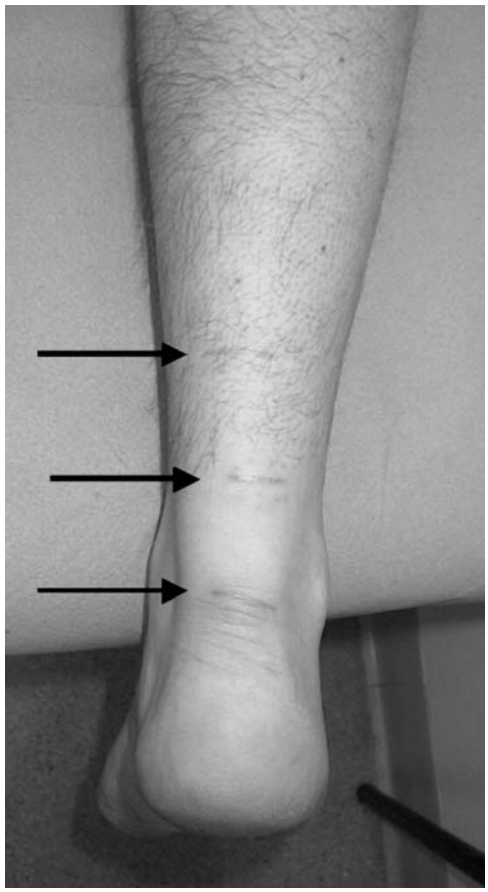

FIGURE 20-5. Appearance of the surgical scars following percutaneous Achilles tendon repair using Webb-Bannister's technique. The arrows point to the 3 transverse wounds. Note that the most proximal one lies slightly more medial than the others.

In summary, there seem to be many advantages from surgical repair, such as precise alignment of the torn tendon, early active mobilization, and excellent functional results with less chance of rerupture and superior strength, while the main disadvantage of open repair is the risk of skin wound problems. Conservative management leads to Achilles tendon healing with extensive scarring, which may lead to lengthening of the tendon and subsequently suboptimal push-off strength.

In conclusion, management of Achilles tendon ruptures should be individualized according to the concerns and health of the patient. If optimal performance is required in patients with high levels of physical activity or athletes, operative management is probably the treatment of choice.

Management of Chronic Achilles Tendon Rupture

More than 20% of patients with Achilles tendon ruptures are missed at initial physical examination [103]. It is usually possible to suture the tendon stumps in an end-to-end fashion within 72 hours of the injury. In chronic ruptures, the tendon stumps cannot be approximated without undue tension. It is not known when an acute rupture becomes chronic, although 4 to 6 weeks seems to be the agreed figure [110].

In chronic ruptures, the gap can be bridged with a single central or 2 (one medial, one lateral) gastrocnemius fascial turndown flaps. If available, the tendon of the plantaris longus can be used as a reinforcing membrane [111]. Where the gap resulting from the rupture does not allow direct suture, other tendons can be used.

Abraham and Pankovich advocated the use of an inverted V-Y sliding myotendinous flap in the proximal portion of the tendon to lengthen it [112].

Perez-Teuffer described detaching peroneus brevis tendon from the base of the fifth metatarsal and then tunneling it through the calcaneum. A modified technique was later used by Turco et al. to treat 40 individuals [113]. Both authors did not report any functional deficit following this operation [114,115] (see Figure 20-6).

Mann et al. reported excellent or good results in 6 patients and fair results in one patient who were treated with the flexor digitorum longus (FDL) as a graft to bridge a large gap between the proximal and distal stumps of ruptured Achilles tendon. The FDL was transected just proximal to the division of the individual tendons and pulled through a drill hole in the calcaneus before using it to bridge the Achilles tendon stumps [116]. More recently, Wapner et al. [117,118] transferred the tendon of flexor hallucis longus to provide a dynamic repair. They followed 7 patients with a mean age of 52 years for an average of 17 months (range 3 to 30 months). There were no postoperative infections, skin losses, or reruptures. Each patient developed a small (but of no functional significance) loss in range of motion in the involved ankle and hallux. All patients were satisfied with the functional results, although one required a molded foot-ankle orthosis for prolonged walking.

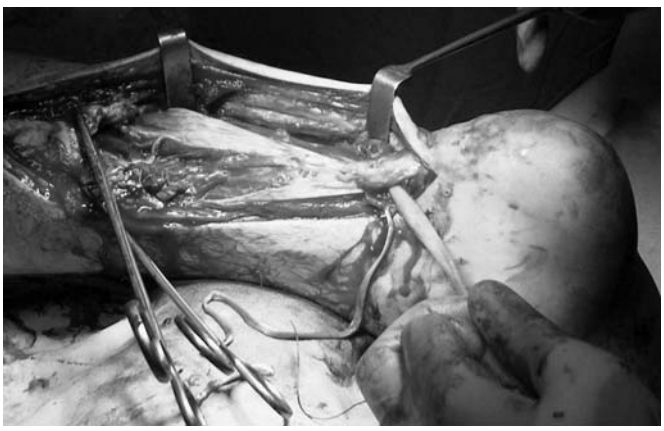

FIGURE 20-6. Peroneus brevis transfer for neglected rupture of the Achilles tendon. The small arrow points to the tendon of plantaris, which in this patient was also used as a reinforcement. The larger arrows point at the tendon of peroneus brevis, which has been passed through the distal stump of the Achilles tendon.

Carbon fiber and polyester fiber implants Marlex or Dexon mesh [119] and grafted tendon covers can be used to bridge the gap when the tendon ends cannot be juxtaposed. Ozaki et al. reported good result following reconstruction of the neglected Achilles tendon rupture using Marlex mesh on 6 patients [120]. They also claimed that Marlex mesh produces less adhesion with neighboring tissues and minimal signs of foreign-body reactions However, synthetic meshes initiate a significant foreign-body reaction in the early stage of collagen scaffolding by forming large edematous areas within the neotendon [121]. Therefore, a more conservative postoperative management of these patients is recommended, restricting their weightbearing and keeping them in plaster for 8 instead of 6 weeks [122].

Bugg et al. placed a 7.5 × 15 cm fascia lata graft obliquely across the Achilles tendon defect, wrapping the remaining around the defect in a tubelike fashion. They reported good result in 10 patients [123].

Postoperative Care

Patients can be discharged the same day or the day after the operation, after having been instructed to use crutches by an orthopedic physiotherapist. Patients are allowed to bear weight on the operated leg as tolerated, but should be told to keep the affected leg elevated for as long as possible to prevent postoperative swelling. Patients are followed on an outpatient basis at 2-week intervals, and the cast is removed 6 weeks after the operation [124–126]. If a cast with the ankle in equinus is applied, it is changed, putting the ankle in gradually increasing dorsiflexion, up to plantigrade, after 2 and 4 weeks, removing the cast altogether six weeks after the operation.

Patients are allowed partial weightbearing and gradual stretching and strengthening exercises, increasing to tolerance, only after removal of the cast. Gradually, patients proceed to full weightbearing 8 to 10 weeks after surgery. During the period in cast, patients are instructed to perform gentle isometric contractions of the gastroc-soleus complex after weightbearing has become comfortable. After removal of the cast, patients mobilize the ankle under physiotherapist guidance. Cycling and swimming

are started 2 weeks after removal of the cast, continuing the ankle mobilization exercises. Patients are prompted to increase the frequency of their self-administered exercise program. Patients are normally able to return to their sport in the fourth postoperative month.

Postoperative Management in Athletes

In athletes and well-motivated, reliable patients, consideration should be given to avoiding immobilization of the ankle. In these patients, an anterior below-knee, plaster-of-Paris slab is applied with the ankle in gravity equinus. Patients are discharged the same day or the day after the operation, and are allowed to toe-touch weightbear on the operated limb as tolerated. They are to keep the operated leg elevated for as long as possible, and are seen 48 to 72 hours after the operation in the plaster room. By this time, the postoperative swelling, if any, has significantly decreased, and the anterior below-knee, plaster-of-Paris slab is changed to an anterior below-knee synthetic slab with the ankle in gravity equinus. The slab is kept in place by an elastic bandage, which allows plantar flexion of the ankle, while dorsiflexion is limited by the footpiece of the slab. Patients are allowed weightbearing as able, using crutches. The slab is changed at the second postoperative week. The limitation of dorsiflexion is continued until the sixth week, when the slab is removed. High-level, well-motivated athletes are compliant, and are normally able to return to some training 6 to 8 weeks after the removal of the anterior slab. A hinged orthosis could be used as an alternative to the anterior slab. However, it is more expensive than simple synthetic cast, although it could be reusable.

Solveborn and Moberg [127] prospectively studied 17 treated patients (15 men and 2 women) who underwent surgical repair of subcutaneous, complete, acute Achilles tendon ruptures. The patients underwent a new postoperative regimen that allowed free ankle motion in a patellar tendon–bearing plaster cast with a protecting frame under the foot allowing weightbearing immediately after surgery. Early free ankle motion after repair of Achilles tendon ruptures proved safe, with satisfactory clinical results. A recent trend toward a more functional rehabilitation program is gaining popularity. These protocols use an anterior plaster slab or an orthosis/walking cast.

Summary

The increased popularity of recreational sporting activities has increased the incidence of Achilles tendon ruptures. These usually occur in sedentary males in their 30s or 40s. Although history and clinical examination are usually sufficient to diagnose acute ruptures of the Achilles tendon, long-standing ruptures may require ultrasonography and/or MRI. Conservative management should be reserved for older patients. Recent rehabilitation protocols have facilitated recovery from operatively and nonoperatively treated Achilles tendon injuries.

Conclusions

The etiology of this common condition is still not completely clarified. Despite extensive investigation, few definitive answers have been found.

The management for acute Achilles tendon ruptures rests with the preference of individual surgeons. Open operative repair probably produces superior functional results compared to nonoperative treatment, but may lead to a higher rate of postoperative complications. Nonoperative management may result in poorer functional results, but the problems of postoperative complications are avoided.

A major problem has been the lack of a universally accepted scoring system for the evaluation of results of management of Achilles tendon rupture. Leppilahti et al. [128] have proposed a scoring scale, and included clinical factors and isokinetic strength evaluation. However, it has been used only by these authors, and isokinetic dynamometry is time consuming, expensive, of dubious reliability, and not widely available.

If the studies reporting a rising incidence of Achilles tendon rupture are accurate, the field of Achilles tendon surgery will become an increasingly important one for orthopedic surgeons. Future developments may include the use of adhesives in tendon surgery [129]. An understanding of the role that cytokines play in tendon healing [130] may also lead to the advent of new treatments, possibly based on gene therapy [131]. However, such novel interventions are unlikely to be in routine clinical use for some time.

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21
Achilles Tendinopathy

Deiary Kader, Nicola Maffulli, Wayne B. Leadbetter, and Per Renström

Introduction

The Achilles tendon is a common source of disability in many athletes due to continuous, prolonged, intense functional demands imposed on it. The prevalence of Achilles tendinopathy is about 11% in runners, 9% in dancers, and less than 2% in tennis players [1–4].

Tendinopathy is a clinical condition characterized by pain and swelling in and around degenerative tendons, arising from overuse [5]. The condition is not only restricted to athletes. 25% to 30% of those affected are nonathletes who may lose significant numbers of working days and have a massive financial impact on society by adding substantially to workers compensation costs [6]. The management of Achilles tendinopathy lacks evidence-based support, and tendinopathy sufferers are at risk of long-term morbidity with unpredictable clinical outcome [7].

Anatomy

The confluence of the gastrocnemius and soleus muscles forms the Achilles tendon. The gastrocnemius is more superficial and originates from 2 heads above the knee. The soleus is anterior to the gastrocnemius and originates below the knee. The plantaris muscle, present in approximately 90% of the population, has a short muscle belly of 7 to 10 cm, arises just below the lateral head of gastrocnemius, and has a long slender tendon that runs medial to the Achilles tendon.

There are 2 bursae at the calcaneal insertion of the Achilles tendon. A subcutaneous bursa lies superficial to the tendon and the skin, and a retrocalcaneal bursa lies between the tendon and the calcaneum.

The Achilles tendon derives its sensory nerve supply from the nerves of the attaching muscles and cutaneous nerves, in particular the sural nerve [8,9].

Histology

The cells in a normal Achilles tendon are well organized. Tenocytes and tenoblasts form up to 95% of the cellular element of the tendon [10]. Specialized fibroblasts, the tenocytes, appear in transverse sections as stellate cells, possibly due to the uniform centrifugal secretion of collagen [11]. Tenoblasts have variable shapes and sizes, and are arranged in long parallel chains [12].

Collagen constitutes about 90% of tendon protein, or approximately 70% of the dry weight of a tendon [9]. The collagen fibers are tightly packed in parallel bundles (13). Type I collagen is the commonest; it forms 95% of tendon collagen, and is held in parallel bundles by small proteoglycan molecules [11]. Elastin accounts for only about 2% of the dry mass of tendon (9) and can undergo up to 200% strain before failure.

Aging significantly decreases tendon glycosaminoglycans and increases collagen concentration [14]. Acute exercise increases type I collagen formation in peritendinous tissue [15].

From a histological viewpoint, tendinopathic areas are characterized by tendinosis. Tendinosis is intratendinous noninflammatory collagen degeneration with fiber disorientation, relative absence of functioning tenocytes, scattered vascular ingrowths and increased interfibrillar glycosaminoglycans [7,9,16,17]. Areas affected by tendinosis show variation in cellular density, probably depending on the duration of symptoms. Some areas of the tendon may contain fatigued tenocytes which have lost their reparative ability [7,18,19]. A typical finding in tendinosis is the increase in the amount of interfibrillar glycosaminoglycans, which may explain the reduced interfiber cohesion of collagen bundles [16]. Microscopically the collagen fibers are disrupted, disorganized, and lacking reflectivity under polarized light (see Figure 21-1). This is associated with an increase in the amount of mucoid ground substance [20].

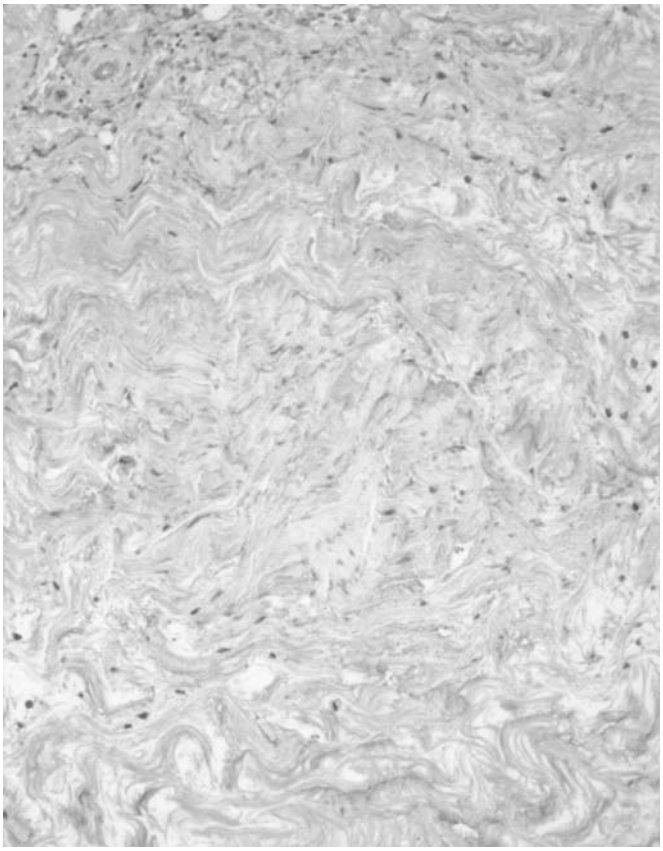

Figure 21-1. Histological appearance of advanced Achilles tendinopathy. Note the hypercellularity, the disorganization of the matrix, and the disruption of the collagen bundles.

Paratenonitis, an inflammation of the paratenon only, generally occurs in the early phases of tendinopathy, and may present as "peritendinitis crepitans" due adhesion between the tendon and paratenon [21].

Tendons receive their blood supply at 3 places: the musculotendinous junction, along their length from the surrounding connective tissue, and at the bone-tendon junction [22]. Although it is common believed that the Achilles tendon may be poorly vascularized in the mid-portion [22], Astrom et al. [23], using laser Doppler flowmetry, showed that there is even blood flow throughout the Achilles tendon, apart from the distal insertion. They also showed that blood flow was higher in women and in symptomatic tendinopathy patients comparing to control. However, tendon blood flow diminishes with increasing age.

Tendons and ligaments have 7.5 times lower oxygen consumption compared to skeletal muscles [24]. Dynamic loading of the Achilles tendon accelerates inflammatory activity and metabolism of lipid and carbohydrate in the peritendinous region [25].

Etiology

The etiology of Achilles tendinopathy remains unclear. There are various theories linking tendinopathies to overuse injuries, poor vascularity, genetic makeup, gender, and endocrine or metabolic factors [7,26].

Excessive loading of the Achilles tendon during vigorous training activities is regarded as the main pathological stimulus that leads to tendinopathy [6], possibly as a result of imbalance between muscle power and tendon elasticity. The Achilles tendon may respond to repetitive supraphysiological overload by either inflammation of its sheath, or degeneration of its body, or a combination of both [27]. Intensive eccentric repetitive loading of the Achilles tendon may affect collagen crosslinking, extracellular tendon matrix, and vascularity.

Tendinopathy has been attributed to a variety of intrinsic and extrinsic factors. Tendon vascularity, gastrocnemius-soleus dysfunction, age, gender, body weight and height, pes cavus deformity, and lateral ankle instability are common intrinsic factors. Changes in training pattern, poor technique, inadequate warm-up and stretching prior to training, previous injuries, footwear, and environmental factors like training on hard, slippery, or slanting surfaces are extrinsic factors [6,21,26,28].

Clinical Aspects

A detailed history helps to identify the onset and possible contributing factors in a painful Achilles tendon. The duration of pain and its relationship to various activities should be documented. The clinical grading of the pain associated with tendinopathy can be useful especially when combined with visual analog scales. However, these scales also have limitations [29]. In athletes, it is crucial to know the frequency and the intensity of training. Errors in training technique should be recognized. A common training error associated with tendinopathy is an abrupt change in the exposure to load or use: Such transition risk has been well described, and may represent either an exhaustion of soft tissue cellular adaptation or a mechanical failure response to the rapid ramp up of load affecting the matrix integrity (30). Finally, the clinician should ask about previous treatment received.

Mild Achilles tendinopathy presents as pain 2 to 6 cm proximal to the tendon insertion after exercise. As the pathological process progresses, pain may occur during exercise. In severe cases, the pain interferes with activities of daily living [31]. There is good correlation between the severity of the disease and the degree of morning stiffness [21]. Runners classically report pain at the beginning and at the end of their training session, with a pain-free period in the central part of their training session [32].

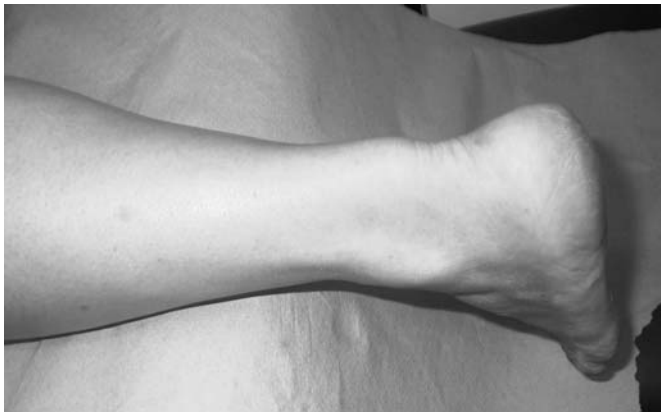

FIGURE 21-2. Typical nodule in Achilles tendinopathy. It is easily appreciated with the patient prone, and is located 2–6 cm proximal to the tendon insertion on the calcaneum.

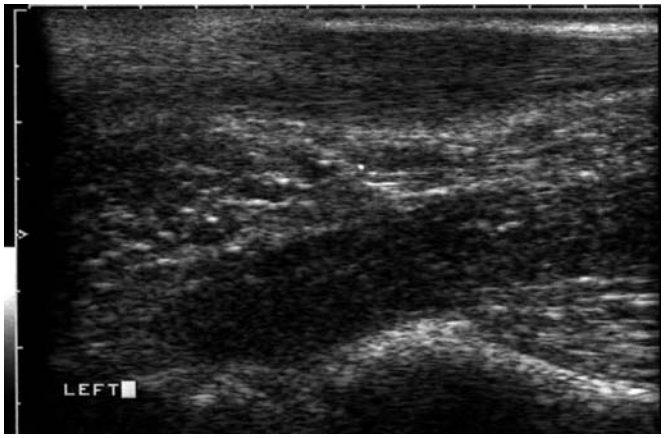

FIGURE 21-3. Preoperative ultrasound scan of the patient whose histological appearance is shown in Figure 21-1. Note the widening of the Achilles tendon and the intratendinous disorganization.

Clinical examination is the best diagnostic tool. Both legs are exposed from above the knees and the patient examined while standing and prone. The foot and the heel should be inspected for any malalignment, deformity, obvious asymmetry in the tendons size, localized thickening, Haglund heel, and any previous scars (see Figure 21-2). The Achilles tendon should be palpated for tenderness, heat, thickening, nodule, and crepitation [4]. The tendons excursion is estimated to determine any tightness. The "painful arc" sign helps to distinguish between tendon and paratenon lesions. In paratendinopathy, the area of maximum thickening and tenderness remains fixed in relation to the malleoli from full dorsi- to plantar flexion, whereas lesions within the tendon move with ankle motion [33]. There is often a discrete nodule, whose tenderness significantly decreases or disappears when the tendon is put under tension [28,34].

Imaging

Although plain soft tissue radiography is no longer the imaging modality of choice in tendon disorders, it still has a role in diagnosing associated or incidental bony abnormalities. Magnetic resonance imaging (MRI) provides extensive information about the internal morphology of tendon and the external anatomy. It is a useful tool to evaluate the various stages of chronic degeneration and differentiation between paratendinopathy and tendinopathy of the main body of the tendon. Areas of mucoid degeneration in the Achilles tendon are shown at MRI as high signal intensity zone on T1 and T2 weighted images.

MRI is superior to ultrasound (US) in detecting incomplete tendon rupture [35,36]. However, due to the high sensitivity of MR imaging, the data should be interpreted with caution and correlated to the patient symptoms before making any recommendations [26]. Although ultrasonography is operator-dependent, it correlates well with histopathologic findings [37] (see Figure 21-3). Many authors regard it as a primary imaging method. Thickening of the Achilles tendon is easily detected with both methods. Only if US remains unclear should an additional MR study be performed and, together with the clinical diagnosis, indications for surgery can be made more efficiently [38]. One of the main advantages of US over other imaging modalities is the interactive facility, which helps reproduce symptom by transducer compression and concentration on the pathologic area [39]. Although US can demonstrate alterations in the Achilles tendon with high specificity and sensitivity it has, like MR imaging, a relatively high incidence of false positive findings [26,40].

Management

At present, management of tendinopathy is more an art than a science [41]. Over the years, various treatment programs have been tried. Most of them essentially follow the same principles. However, very few randomized, prospective, placebo-controlled trials exist to assist in choosing the best evidence-based treatment.

In chronic tendinopathy, the results of treatment are less predictable [42–44]. Therefore, it is important to encourage athletes to follow a correct training program [45] and to educate them to seek medical advice at the early stages to prevent tendinopathy in the first place.

Nonoperative Management

Up to 98% success rates have been reported following comprehensive nonoperative protocols including rest, anti-inflammatory drugs, physiotherapy and orthosis [46].

Complete abstention from running and weightbearing sporting activities is often recommended in the acute phase, while in mild tendinopathy relative rest or modified activities are prescribed, with reduction of the running distance or the training duration [47]. Collagen fiber repair and remodeling is stimulated by tendon loading. Therefore, complete rest of an injured tendon is counterproductive.

Deep friction massage is regarded as a most important technique to break down adhesions in paratendinopathy [48]. In chronic tendinopathy, this should be accompanied by stretching to restore tissue elasticity and reduce the strain in the muscle-tendon unit with joint motion.

Eccentric loading of fatigued muscle may lead to microtrauma, which triggers Achilles tendinopathy with paratendinopathy [46]. Therefore, eccentric strengthening of the gastroc-soleus muscle complex and loading of the Achilles tendon are important for both prevention and management of chronic tendinopathy [49–51].

A heel lift of 12 to 15 mm is another widely recommended treatment for Achilles tendon pain [46], but Lee et al. [52] advocated heel lifts of 1.9 to 5.7 cm to relax the calf muscles and decrease the tension on the Achilles tendon during normal level walking.

Cryotherapy (e.g. icing) promotes tendon healing by reducing the metabolic rate of tendon and decreasing the extravasation of blood and protein from the new capillaries found in tendinosis [53].

Various forms of electrotherapy are commonly used for the management of tendinopathy, with very little evidence to substantiate their efficacy [54]. Theoretically, ultrasound decreases swelling in the acute inflammatory phase and improves tendon healing [54,55]. US increases both the tensile strength and the energy absorption capacity of the tendons in rabbits, and may expedite healing in surgically repaired Achilles tendon [56]. US also stimulates collagen synthesis in tenoblasts and cell division during periods of rapid cell proliferation [57]. Owoeye et al. [58] used low-intensity, pulsed galvanic currents on tenotomized rats Achilles tendons. They showed that the group treated with anodal current withstood significantly greater loads than the group treated with cathodal current or healed normally (i.e. without stimulation).

Although Read and Motto [59] found that local injection of the Achilles tendon with steroids have no deleterious effect on outcome, there is insufficient evidence comparing the risks and benefits of corticosteroid injections in Achilles tendinopathy [60,61]. Intratendinous injections of steroid in animal studies showed reduction in tendon strength with a potential risk of rupture for several weeks following injection [20,60,62,63].

Several other drugs, such as low-dose heparin, glycosaminoglycan, and aprotinin have been used in the management of peri- and intratendinous pathology [64,65].

Operative Management

Surgery is recommended to patients in whom nonoperative management has proved ineffective for at least 6 months. From 24% to 45.5% of the patients with Achilles tendon problems fail to respond to conservative treatment and eventually require surgical intervention [66–70]. Paavola et al. [68] in a prospective long-term follow-up study showed that the prognosis of patients with acute to subchronic Achilles tendinopathy treated nonoperatively is favorable, and, at an average 8 years after surgery, 94% of the patients were asymptomatic or had mild pain with strenuous exercise.

There are minor variations in surgical technique for tendinopathy [33,71–80]. Nevertheless, the objective is to excise fibrotic adhesions, remove degenerated nodules, and make multiple longitudinal incisions in the tendon to detect intratendinous lesions and to restore vascularity, and possibly stimulate the remaining viable cells to initiate cell matrix response and healing [16,27,37,81,82]. Most authors report excellent or good results in up to 85% of cases.

Management of peritendinitis includes releasing the crural fascia on both sides of the tendon. Adhesions around the tendon are then trimmed; the strongly hypertrophied portions of the paratenon are excised [67]. In tenolysis, classically longitudinal tenotomies are made along the longitudinal axis of the tendon in the abnormal tendon tissues excising areas of mucinoid degeneration. Reconstruction procedure may be required if large lesions are excised [83].

Operative Technique

The operation is performed on an outpatient basis. The patient is examined preoperatively to correctly identify and mark the area of maximum tenderness and swelling. Ultrasound scanning could be used to confirm the precise location of tendinosis and paratendinitis. The patient lies prone with the ankles resting on a sandbag or a pillow and the feet dependant over the end of the operating table. We normally do not use a tourniquet, but lift the end of the operating table 15 to 20 degrees. A longitudinal curved incision, with the concave part toward the tendon, is centered over the abnormal part of the tendon (see Figure 21-4). Placing the incision medially avoids injury to the sural nerve and short saphenous vein, and medial curvature prevents direct exposure of the tendon in case of skin breakdown [21,84].

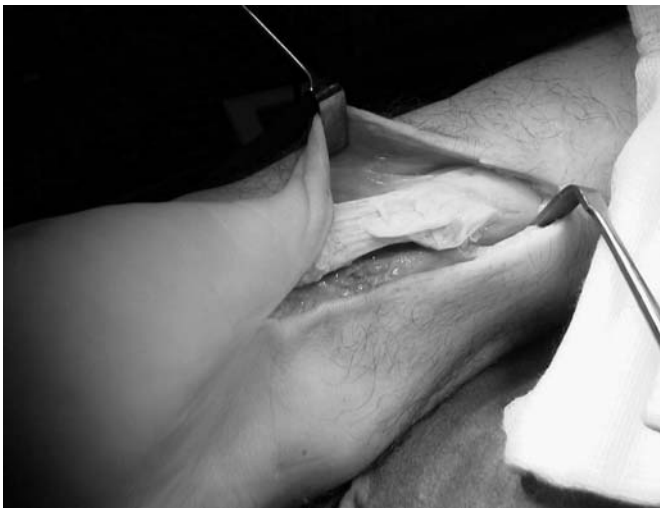

FIGURE 21-4. Intraoperative picture of a patient with advanced disruption of the Achilles tendon. Note the advanced degeneration with loss of continuity of the tendon fibers, and the hypertrophic paratenon.

The paratenon and crural fascia are incised and dissected from the underlying tendon. If necessary, the tendon is freed from adhesions on the posterior, medial, and lateral aspects. The paratenon should be excised obliquely as transverse excision may produce a constriction ring, which may require further surgery [33]. It is important not to disturb the fatty tissue in Kager's triangle anterior to the tendon, as the mesotendon contained within it is an important source of vascular supply to the tendon. Areas of thickened, fibrotic, and inflamed tendon are excised. Inspection for areas lacking normal luster, and careful palpation for thickening, softening, or defects will reveal the tendon portion corresponding to areas of tendinosis. These zones can be explored with longitudinal tenotomies. The pathology is identified by the change in texture and color of the tendon. The lesions are then excised, and the defect can either be sutured in a side-to-side fashion or left open: we normally leave it open. If extensive debridement is required, it is possible to use a turned-down flap of the aponeurosis of the medial or lateral head of the gastrocnemius to repair the defect. If present, the plantaris tendon can be used to reinforce the tendon either by weaving it within the tendon or as a reinforcing membrane. In most cases, lesions will be well localized, with normal tendon in between. Hemostasis is important, since the reduction of postoperative bleeding speeds up recovery and diminishes any possible fibrotic inflammatory reaction.

In patients with an insertional lesions or retrocalcaneal bursitis, an extended medial approach is used. A full inspection may reveal an enlarged, inflamed or scarred retrocalcaneal bursa, adherent to the anterior surface of the Achilles tendon. There may be, in addition, fluid or loose fibrinous bodies within the bursa. After excision of this area, inspection of the posterior superior angle of the calcaneum allows visualization of any impingement with the insertion of the Achilles tendon with dorsiflexion. This area can be removed with an osteotome, and the sharp edges removed with a rasp. If used, the tourniquet can be deflated, and hemostasis achieved by cautery. A below-knee, lightweight cast or orthosis is applied with the foot plantigrade, allowing early mobilization [85].

Postoperative immobilization is implemented for 2 weeks encouraging the patient to bear weight as soon as they are comfortable and able to do so. Greater protection is recommended in patients who underwent reconstruction. At about 2 to 6 weeks, stretching exercises are started. Sport-specific training is stated at 3 months, and competition is resumed at 6 months.

Innovative Operative Procedures

Percutaneous Longitudinal Tenotomy

In patients with isolated Achilles tendinopathy with no paratendinous involvement and a well-defined, nodular lesion less that 2.5 cm long, we have used multiple percutaneous longitudinal tenotomies when conservative management has failed. An US scan can be used to confirm the precise location of the area of tendinopathy. The skin and the subcutaneous tissues over the Achilles tendon are infiltrated with 10 mL of plain 1% Lignocaine. A number 11 scalpel blade is inserted parallel to the long axis of the tendon fibers in the marked area(s) with the cutting edge pointing cranially. Keeping the blade still, a full passive ankle dorsiflexion movement is produced. After reversing the position of the blade, a full passive ankle plantar flexion movement is produced. A variable, but approximately of 3 cm long, area of tenolysis is thus obtained through a stab wound. The procedure is repeated through 4 other stab incisions at 2 cm medial and proximally, medial and distally, lateral and proximally, and lateral and distally to the site of the first stab wound. The 5 wounds are closed with Steri-Strips, and dressed with cotton swabs. A few layers of cotton wool and a crepe bandage are applied. Patients are mobilized as soon as able [86].

If the multiple percutaneous tenotomies are performed in the absence of chronic peritendinopathy, the outcome is comparable to that of open procedures. In addition, it is simple, and can be performed in the clinic under local anesthesia without a tourniquet. Attention to details is necessary, as even in minimally invasive procedures complications are possible.

Muscle Transfer to the Body of the Tendon

Recent experimental evidence shows that longitudinal tenotomies increase the blood supply of the degenerated area [87]. Recently, in a rabbit model, following longitudinal tenotomy, we have implanted a soleus pedicle graft within the operated tendon, and shown that the transplanted muscle was viable and had integrated well within the tendon tissue 3 months after the transplant, without transforming into connective tissue. The transplanted muscle fibers thus integrate with the tendon but remain distinct from it. Hypervascularization of the graft tissue, probably due to the operation, was also observed, together with neoangiogenesis up to 3 months after the operation [88].

Summary

1. Clinicians and therapist should unify their terminology and use the term tendinopathy to clinically describe tendon conditions.
2. Correct exercise and training technique is crucial for the prevention of Achilles tendinopathy.
3. At early stages, Achilles tendinopathy could be successfully treated nonoperatively in 2 to 3 months, while long standing chronic tendinopathy is more difficult to treat and may require 4 to 6 months to recover.
4. Nonoperative treatment relies primarily on appropriate tendon loading. This can be achieved by activity modification and by biomechanical correction. Relative rest, heel lift, cryotherapy, deep friction massage, and electrotherapy are all used with variable success rate. The benefit of steroid injections has not been consistently documented.
5. Imaging is recommended only when the diagnosis is unclear, as it has not been shown to be a useful guide to management or prognosis. A focal hypoechoic region on US, or a region of high signal on MR do not constitutes, per se, an indication for surgery.
6. Surgery is recommended if nonoperative treatment for 3 to 6 months is unsuccessful.
7. The objective of surgery is to improve local circulation and stimulate natural healing process. The procedure involves removing adhesions, inflamed and degenerated areas with tendon decompression through fasciotomy and longitudinal tenotomies.
8. It takes between 6 and 12 months to return to full competitive sport after successful Achilles tendon surgery. However, full recovery to prior levels of performance is not predictable in any one individual and are dependent upon variables of repair and rehabilitation. Therefore, expectations should be cautiously optimistic.

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Part III
Management of Tendon Injuries

22
Anti-Inflammatory Therapy in Tendinopathy: The Role of Nonsteroidal Drugs and Corticosteroid Injections

Wayne B. Leadbetter

Anti-inflammatory therapy is commonly prescribed for the treatment of musculoskeletal soft tissue injury and tendinopathy [1–6]. Since either acute macrotraumatic or chronic microtraumatic injury is often associated with pain, stiffness, swelling, and loss of function, historically cardinal signs of an inflammatory process, nonsteroidal anti-inflammatory drugs (NSAIDs) and a variety of synthetic derivatives of cortisol, an adrenal glucocorticoid, have achieved widespread endorsement [1,7]. The popularity of these agents testifies to the prevalent belief that such medical intervention can relieve the initial disability and improve the rate of recovery from injury. This utilization pattern has been documented by surveys revealing that more than 17 million Americans consume NSAIDs daily, and some 50 million Americans use NSAIDs intermittently or routinely yearly; up to 30 million of the elderly take NSAIDs on a regular basis [8]. In a random survey of 400 orthopedic surgeons, 90 used steroid injection in the treatment of their patients, administering an average of 193 extra-articular injections annually, most primarily for bursitis and tendinopathy [9].

Such popular clinical treatment patterns persist despite serious potential gastrointestinal, renal, and cardiovascular side effects [10–13]. The issue is additionally compounded by concerns centering on difficulties in substantiating the degree of clinical benefit achieved by such treatment [14,15]. This chapter provides an overview of the pharmacologic effects, current therapeutic rationale, prescription guidelines, potential side effects, and known efficacy of these potential anti-inflammatory drugs. The reader's attention is drawn to the relevant features of the pathophysiology and healing of tendinopathy and paratendinopathy, and the implications to such therapeutic intervention.

Tissue Response to Tendon Injury

Because the most common objectives of anti-inflammatory therapy in tendon injury are the relief of excessive pain and inflammation, the following brief discussion may prove useful in forming a rationale for such treatment. Injury is characterized as acute (i.e. macrotraumatic) or chronic (i.e. microtraumatic, overuse, cumulative trauma, or repetitive motion disorder) [16,17]. Acute human tissue response is characterized by three phases: 1) acute vascular-inflammatory; 2) repair-regeneration; and 3) maturation [18]. In normal tissue healing, inflammation plays an important initial role in this complex dynamic process. The resulting restoration of anatomic tissue continuity is the product of an orderly, progressive, and interdependent biologic repair sequence. In this context, inflammation is often defined as a normally occurring, localized protective response that serves to destroy, dilute, or wall off the injurious agent, the injured tissue, and the byproducts of such injury [25]. Acute inflammation is characterized by the classic signs of pain (dolor), heat (calor) redness (rubor), swelling (tumor), and loss of function (functio laesa) [16]. The latter characteristic provides the primary impetus in the treatment of tendon injury in recreation or the workplace. Histologically, acute inflammation involves a series of interactive events, including A) dilatation of arterioles, capillaries, and venules, with increased permeability and blood flow; B) exudation of fluids, including plasma proteins; C) activation and release of immunologically active mediators; D) activation of humeral response mechanisms; and E) leukocytic migration to the inflammatory focus [19] (see Figure 22-1). Subsequent neutrophilic activation results in the so-called "respiratory burst" activity characterized by the generation of high concentrations of oxygen-free

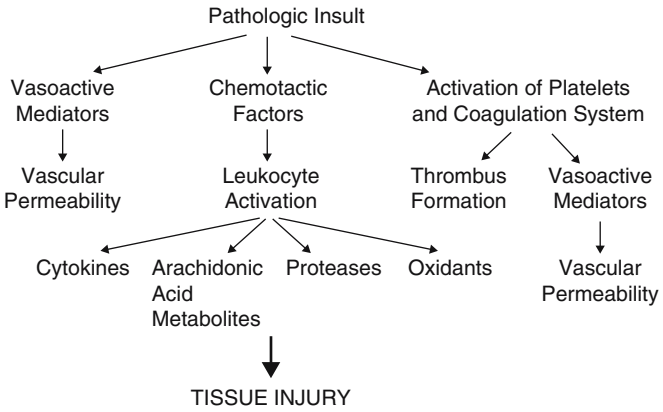


FIGURE 22-1. Mediator events in response to tissue injury. (From Fantone J. Basic concepts of inflammation. In: Leadbetter WB, Buckwalter JB, Gordon SL, eds. *Sports-Induced Inflammation.* Park Ridge, IL: American Academy of Orthopaedic Surgeons, 1990. P. 26, with permission [19].)

radical species (e.g. O_2, H_20_2, OH, HOCL) [17,20]. These free radicals are extremely reactive and chemically unstable. They are known to chemically attack the phospholipase structure of cell membranes by the process of lipid peroxidation, forming unstable lipid peroxide radicals that break down into smaller molecules, leading eventually to the dissolution of the cell wall and the generation of arachidonic acid metabolites. Persistent inflammatory signs and symptoms as well as further posttraumatic tissue damage are directly related to these events. Theoretically, tissue hypoxia caused by vascular disruption in acute injury or intermittent tissue hypoxia that may occur in the cyclic loading of such tissues as tendon may be a stimulus for the cellular release of such oxygen-free radicals. The possible occurrence of such events forms the basis for one of the theoretical models of chronic tendon degeneration [17,19,20].

Tissue degeneration is a dominant finding in chronic tendinopathy complaints. In the great majority of spontaneous tendon ruptures, chronic degenerative changes are seen at the rupture site of the tendon [21]. Multiple factors often catalyzed by overuse and overload, and fatigue may alter the basal reparative ability of injured tendon. Intense cyclic, often eccentric load is thought to lead to cumulative microtraumatic effects, furthering weakening collagen cross-linking noncollagenous matrix elements and vascular elements of tendon [21]. The resulting tendinosis lesion characterized histologically by coexistence of degenerative histologies is presumed to be the result of profound perturbation and dysregulation of reparative fibroblastic activity. The infiltration of lymphocytes and macrophage-type cells is not a dominant feature of this aspect of tendon injury response [22,23].

Inflammation may be initiated by injury or irritation of vascularized tissues, such as synovium, exposed to excessive mechanical load or use [16]. It is a time-dependent, evolving process characterized by vascular, chemical, and cellular events preceding tissue regeneration, repair, or scar formation [16]. Clinically, soft tissue inflammation may spontaneously resolve or too often may become a major part of the patient's problem. The factors that cause an acute injury to evolve into a chronic inflammatory condition are poorly understood; evidence suggests that continued abuse of load and irritation may stimulate the local release of cytokines, resulting in both autocrine (cell) and paracrine (adjacent cell) stimulation and modulation of further cell activity [19]. So-called failed healing responses or the abortion of the normal orderly healing progression in a wound often lead to granulation tissue formation or tissue degeneration (i.e. a damaged or less functionally capable tissue) [16]. The aging process contributes to a tendency toward the chronic injury condition [24].

In paratendinopathy, evidence is increasing in both acute and chronic synovitis for the role of immunologically mediated amplification, as well as propagation, which may itself lead to further tissue damage. Material to be eliminated (i.e. antigen) is recognized as being "foreign" by specific or nonspecific means [25]. Specific recognition is mediated by immunoglobulins (i.e. antibodies) and by receptors on T lymphocytes that bind to specific determinates (epitopes). For instance, activated T-cell populations and monocyte-macrophage populations have been identified in non-septic olecranon bursitis [26]. Similar activated T-cell populations have been identified in chronic paratendinopathy [27]. Such findings add credence to an autoimmune mechanism of synovial injury response [28].

Recognition of denatured proteins or nonspecific forms of recognition can be mediated directly by the alternative complement pathway or by phagocytes [28]. Binding of a recognition component of the immune system to an antigen generally leads to activation of an amplification system, initiating production of proinflammatory substances. The actual destruction of antigens by immune mechanisms is mediated by phagocytic cells [25]. In synovial-lined structures, macrophages and related cells (e.g. Kupffer cells, type A synovial lining cells) are central components of this system [25,29,30]. Such inflammatory activations have long formed the basis for the induction of synovial inflammation by articular cartilage matrix molecules released in association with degenerative joint disease, implant particle debris, or chemical agents [30].

Mode of Action and Pharmacologic Effects of Anti-Inflammatory Medication

Laboratory research into the mode of action and effects of anti-inflammatory medications has suffered from significant limitations, both *in vitro* and *in vivo.* Most promi-

nent is the lack of a reliable and consistently reproducible tendinopathy animal model for demonstrating overuse pathology [31,32]. The few that exist suffer from low rates of reproducibility as well as the tendency for spontaneous healing and resolution of the lesion once tissue stimulation ceases [33]. (Garrett, personal communication.)

This is in contradistinction to one of the cardinal characteristics of chronic tendon degeneration—persistence of the lesion. Attempts to create an analogous overuse injury with such agents as collagenase, while producing histologic similarity, lack verification of pathophysiologic comparability to human clinical injury [31]. In the absence of an overuse injury animal model, virtually all research *in vivo* on corticosteroid injection reflects tissue responses of normal tendon to injection challenge. In addition, animals vary considerably in response to anti-inflammatory agents such as corticosteroids [34]. Although many of the original observations regarding the regulatory effects of glucocorticosteroids on immune and inflammatory responses were made in animals, generalization of these findings to humans must be cautious owing to species differences. For instance, immunoregulatory cells in some species, such as the rabbit, mouse, and rat, are lysed by corticosteroids, whereas lymphocytes from other species, such as the guinea pig and human, are resistant to such lytic effects [34]. Discrepancy due to such factors as the age of the animal model, tissue fixation artifacts, and microscopic sampling error add to the difficulty of assessing the literature. To control some of these variables, *in vitro* modeling, such as fibroblast cell monolayer cyclic perturbation, has provided insight, especially into the anti-inflammatory activity of NSAIDs [35]. However, such cell monolayers have been demonstrated to behave quite differently biologically from similar cells grown in a three-dimensional collagen matrix 177. The known *in vitro* models for healing and wound repair are, at best, primitive approximations of what is known to be a multifactorial, codependent, intrinsically augmented event. As has been said, "wounds do not heal in a bottle [36]." This emphasizes the fact that medicine is not practiced in a controlled *in vitro* environment, but rather in the open system of cell- and humeral-mediated responses of the human body.

Notwithstanding the previous observations, both NSAIDs and glucocorticosteroid esters have profound suppressive effects at sites of synovial inflammation, such as joint synovitis, bursitis, and paratenonitis [1,5,6,37,38].

In 1971, Vane first suggested that an inflammatory response is mediated by the accumulation of excessive amounts of prostaglandins [39]. Hypertrophic and hyperplastic synovial tissues demonstrate high levels of prostaglandin synthesis. For instance, rheumatoid synovial tissue, in culture, produces approximately 10 times the level of prostaglandin synthesis.

Products, including PGE-2, thromboxanes, and oxygen-free radicals, are synthesized by phagocytic cells (i.e. polymorphonuclear leukocytes, monocytes, and macrophages) [37,38]. Glucocorticoids have little or no suppressive effect on PGE-1 functions [34]. The claims of COX-2 inhibitor drugs notwithstanding, most nonsteroidal drugs are not selective in suppressing both PGE-1 and PGE-2 effects [6]. This accounts, in large measure, for the broad spectrum of adverse potential side effects of NSAIDs, including decreased cytoprotective mucus formation in the gastrointestinal tract, alterations and impairment of the normal regulation of renal blood flow and water resorption in the kidney, and increased bleeding secondary to decreased platelet adhesiveness [1,10–12].

With the discovery of the two isoforms of a cyclogenase (COX), COX-1 and COX-2 presented an opportunity for selective pharmacologic treatment. Selective COX-2 inhibitors, such as rofecoxib or celecoxib, may suppress pathologic responses mediated by prostanoids (e.g. pain and inflammation) without inducing toxicity associated with the inhibition of COX-1. The antiplatelet effects of nonspecific nonsteroidals are mediated by their role in preventing the conversion of arachidonic acid into thromboxane A2, which is an important pathway of platelet aggregation [40,41,47] (Figure 22.2). Arachidonic acid is converted to thromboxane A2 by the activity of cyclogenase. While the use of COX-2 inhibitors has reduced the risk of increased bleeding in acute soft tissue injury, there remain concerns regarding the effects on soft tissue healing. Elder et al. found a 32% lower load to failure in an acute medial collateral ligament injury experimental model in rats at 14 days after injury. The mechanism for this observation could not be explained, but the study did not support the use of cyclogenase specific inhibitors in the treatment of ligamentous injury [42,43].

Both NSAIDs and corticosteroids exert important effects on inflammatory cells separate from their ability to inhibit prostaglandin synthesis [43,49–51] (Figure 22.3). Reports that nonacetylates (e.g. salicylsalicylic acid), which do not inhibit prostaglandin synthesis, are as effective in rheumatoid arthritis as aspirin has placed new emphasis on these cellular effects [6]. NSAIDs and corticosteroids differ in their manner of cellular interaction. NSAIDs are thought to act by stimulus-response coupling in the cell wall and modulating cell behavior by influencing internal cell secondary messengers [44,45]. At the molecular level, corticosteroids control the rate of protein synthesis by reacting with receptor proteins in the cell cytoplasm [34]. The steroid-receptor complex moves into the nucleus and directs the transcription of RNA and ultimately the synthesis of specific proteins [34]. NSAIDs can inhibit a variety of membrane-associated processes, including superoxide anion generation by a cell-free NADPH oxidase system of neutrophils, mononuclear cell phospholipase C activity, and the 12-hydroperoxyeicosatetraenoic acid peroxidase of the lipoxygenase pathway in platelets (HPETE) [41]. NSAIDs have promi-

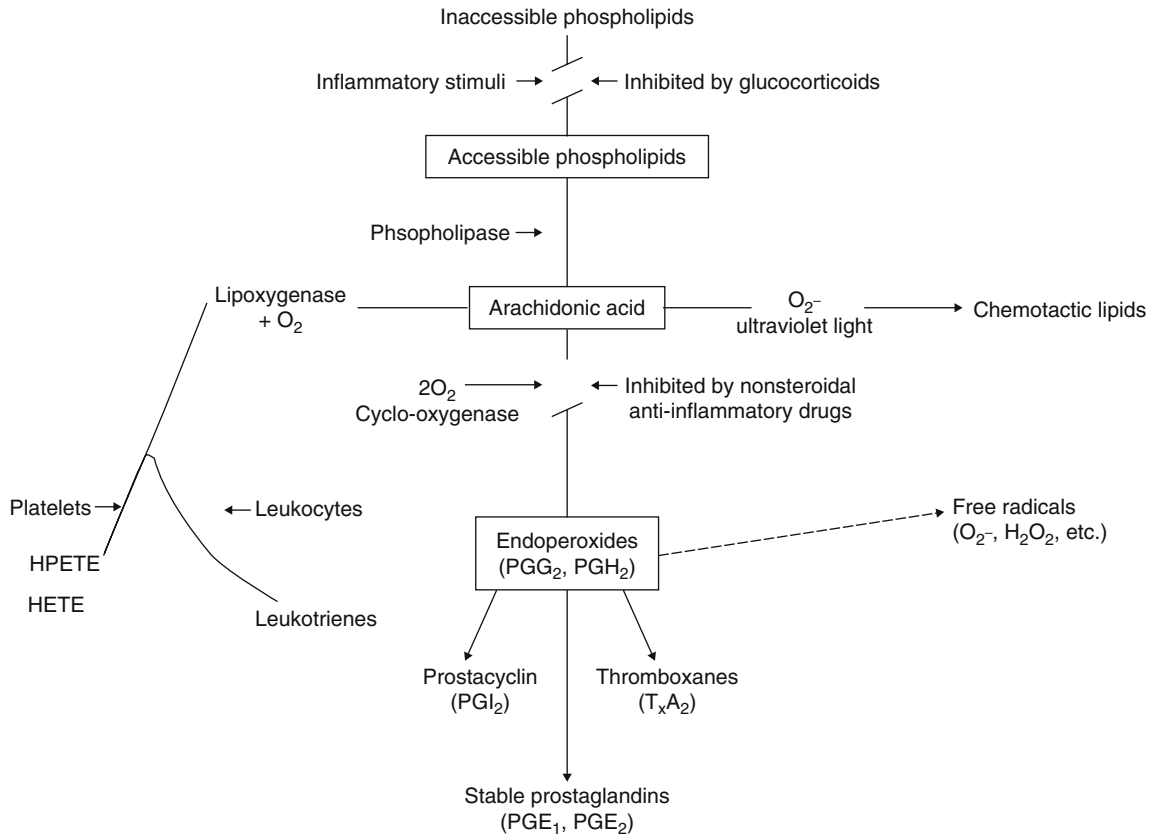


FIGURE 22-2. Arachidonic acid cascade. (From Paulus HE, Furst DE. (1989) Aspirin and other nonsteroidal anti-inflammatory drugs in McCarty DJ, ed. *Arthritis and Other Allied Conditions.* 11th ed. Philadelphia: Lea and Febiger, p. 509, with permission [43].)

nent effects on neutrophil function, including inhibition of aggregation, neutrophil migration, lysosomal enzyme release, oxidative phosphorylation, and chemotactic response [37]. Glucocorticosteroids exhibit similar suppressive effects on the cellular components of inflammation and immunity [34,44]. For instance, using an experimental model for allergic inflammation of the air-pouch type in rats, Kurihara et al. demonstrated that local administration of either dexamethasone or indomethacin inhibited leukocyte infiltration, but that only dexamethasone reduced the chemotactic activity of the exudate [45]. This suggested that anti-inflammatory steroids manifest their inhibitory effect on leukocyte infiltration by inhibiting the generation of chemotactic factors at the inflammatory site. Bjork et al. found that systemic injection with methylprednisolone in the hamster model of immune complex-induced inflammatory reaction produced microvascular leakage only on the venular side of the microcirculation in immunized animals exposed to antigen [46]. The leakage was largely inhibited by treatment with methylprednisolone. The authors proposed a modulation in endothelial cell receptors and function. Such observations help to explain how anti-inflammatory agents also retard granulation tissue response.

Cell perturbation, of which cyclic loading, or so-called microtrauma is a clinical form, results in the

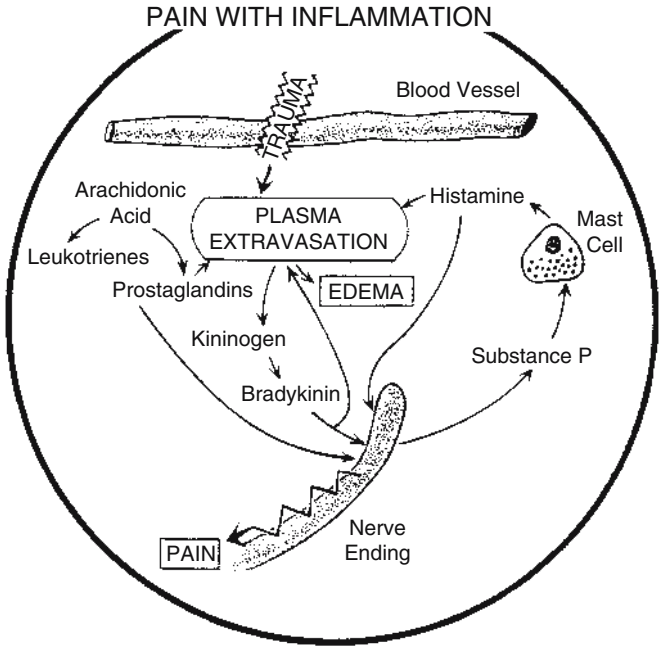


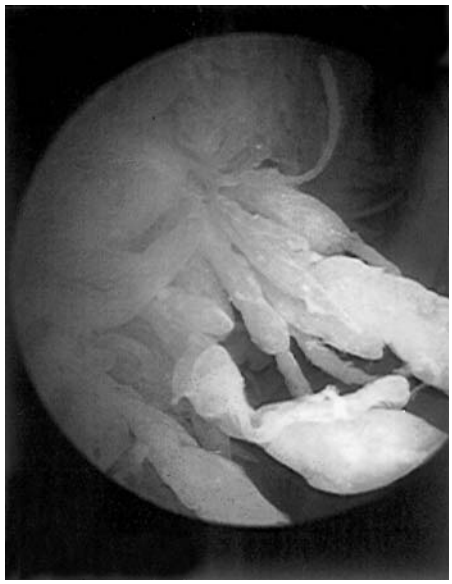
FIGURE 22-3. Schema of the positive feedback relationship that develops during the course of inflammation secondary to sports-related trauma. (From Troulos ES, Dionne RA. (1987) Pharmacologic rationale for the treatment of acute pain. *Dent Clin North Am.* 31:675–694, with permission.)

inflammatory expression and generation of arachidonic acid metabolite by virtually any cell, including tissue parenchymal cells such as the fibro-blast. Almekinders et al. observed increased release of prostaglandin E2, increased deoxyribonucleic acid (DNA) and protein synthesis in response to *in vitro* repetitive motion stimulus of human tendon fibroblast [47]. Hart et al. have called attention to a potential endogenous source of inflammation in tendon based upon dysregulation of neural and roast cell components [48,49]. Hence, in the overuse injury of dense connective tissue structures, subjective pain does not depend upon classic inflammatory histology [18].

However, the evidence for prostaglandin E2 activity in tendinosis is not uniform. Alfredson et al. found no significant differences in the concentrations of prostaglandin E2 between tendons from patients with normal tendon compared with patients with tendinosis lesions based on microdialysis and immunohistochemistry *in vivo*. The results did show significantly higher concentrations of the neurotransmitter glutamate in affected tendons [50]. The fact that the study was performed under resting conditions may explain the difference of inflammatory findings from the previous studies. Thus, the rationale for anti-inflammatory therapy may still include stabilization of cell membrane integrity of all resident tissue cell populations, primarily through the inhibition of the phospholipase A2 enzyme, reducing lysosomal enzyme release and decreasing cellular swelling and edema, in addition to decreasing inflammatory biochemistry.

Whereas the inhibition of prostaglandin synthesis remains a primary function of all NSAIDs, another interesting effect is the finding that some of these agents inhibit the uptake, and thereby slow the breakdown, of a potent vasodilator adenosine [51]. This results in a local dilatation of microvasculature, theoretically providing injured tissue with more oxygen and repair substrates. However, any theoretical speeding of wound healing based on this mechanism, remains unsubstantiated. Decreased adenosine may also diminish pain nociceptor stimulation [51]. The potential disadvantage of increasing local edema, bleeding, and swelling, secondary to such effects, also remains unevaluated. Glucocorticosteroids can modulate the composition of inflammatory actions by inhibiting the release of cytokines, chemical mediators, and enzymes into tissues [34,37]. Local inhibition of activation of various cell types, including the neutrophil, basophil, macrophage, and fibroblast, has been demonstrated [52]. Because the macrophage is a plurifunctional cell that acts as a key source of growth factors to activate fibroblasts during postinjury repair, disruption of these cell functions is another possible mechanism for the clinically observed soft tissue weakening effects of direct corticosteroid injection.

Inflamed synovial tissue is a prime therapeutic target for glucocorticosteroids; therefore, their intrasynovial pharmacologic behavior has been intensely studied [38]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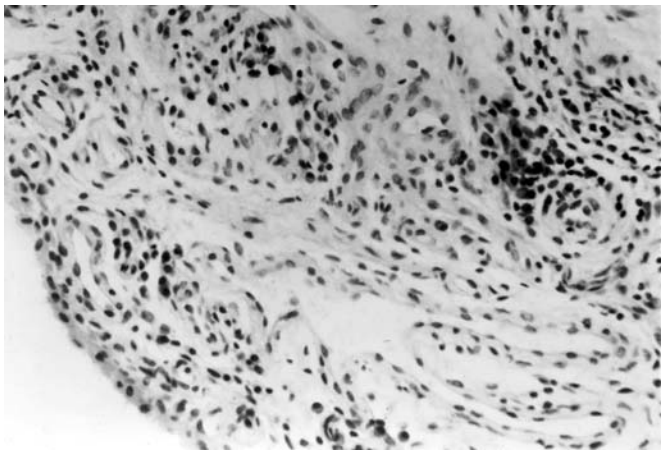
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FIGURE 22-4. (A) An example of hypertrophic synovitis in the knee (arthroscopic view). High levels of prostaglandins make this tissue prime target for anti-inflammatory therapy (See color insert). (B) Hyperptastic and inflamed paratenon synovium (microscopic view 650x).

(Figure 22-4A,B, see color insert). Cortisone and hydrocortisone are highly soluble and cleared rapidly from joint cavities. The half-life of drug samples tagged with carbon-14 varies from 60 to 107 minutes [38]. From 1950 to 1965, progressively less soluble (i.e. longer-acting) corticosteroid esters were synthesized and marketed. Both in dogs and in humans, that the duration of response correlates inversely with the solubility of the preparation in water [53]. For this reason, the least soluble preparation, triamcinolone hexacetonide, is favored for treatment of chronic synovial inflammation [53,54]. Gray and associates [38], in an exhaustive review of parenteral corticosteroid treatment in rheumatoid disorders, noted the following potential modes of action: 1) enhancement of hyaluronic acid concentration and polymerization in synovial fluid; 2) increased viscosity of synovial fluid; 3) fewer leukocytes in the synovial fluid; 4) decreased synthesis of collagenase and prostaglandins;

5) production of a peptide factor that may depress neutrophil migration as well as that of monocytes and macrophages. (This peptide may inhibit the assembly of cytoplasmic microtubules within leukocytes, an effect similar to that with colchicine, and may be mediated indirectly by enhanced intracellular cyclic adenosine triphosphatase.); 6) suppression of cellular immunity in rheumatoid synovium by suppression of T lymphocytes; 7) inhibition of lymphocyte-mediated activities, including lymphokine production, T suppressor cell function, and antibody-dependent cell cytotoxicity; and finally 8) decreasing antibody production, including alterations in immunoglobulin synthesis and complement level. The significance of all of these mechanisms is a subject of ongoing research. Further, the dose of corticosteroid ester used intra-articularly is not proportional to the effect of oral doses because any excess of corticosteroid over the amount that synovial membrane retains is absorbed into the systemic circulation, the optimal amount for local injection is the maximal amount that can be held locally by the tissues [53,54]. Crystalline suspensions may be taken up by synovial lining cells, creating the potential for a true "crystal-induced synovitis [55]." These deposits are eventually inactivated by hydrolysis. Retention of depo preparations in soft tissues is often substantiated by clinical observation at the time of surgery, such as tenolysis, linear tenotomy, or bursectomy. Both the microscopic presence as well as the gross appearance of microcrystalline deposits have been documented. (Leadbetter, unpublished data).

Research on the effects of anti-inflammatory medication, particularly corticosteroids, upon the commonly injured tissues—tendon, ligament, and articular cartilage—has revealed conflicting and often significant deleterious structural effects [4,5,7,56–68]. The persistence and distribution of injected glucocorticosteroids in such tissues have been far less documented than in synovial tissue. Sharing characteristics of hypo vascularity and a highly differentiated parenchymal cell population, these tissues often lack the ideal reparative requirements of adequate vascular supply and the availability of pluripotential cells such as the tissue macrophage [17]. Such characteristics do not lend themselves to spontaneous repair unless increased local blood supply can be induced by significant acute trauma or a surgical manipulation. Injection studies of normal ligament and tendon tissue have documented retardation of the normal, orderly, progressive phases of acute wound healing [65,68]. The majority of evidence suggests that corticosteroids significantly inhibit both the inflammatory and proliferative phases of both tendon and ligament healing with respect to return of both biomechanical properties and histologic maturation, despite some conflicting evidence in the literature [4,5,7,65,68]. NSAIDs have been shown in the laboratory to have both suppressive and stimulatory effects on healing ligament and upon articular cartilage metabolism [69,70].

In a recent review, Almekinders [47] noted the paucity of laboratory data regarding NSAIDs in sports-injured soft tissue. As early as 1977, Vogel [69] had shown that aspirin, phenylbutazone, and indomethacin were able to increase strength in a variety of uninjured collagenous structures in rats. This was attributed to a higher degree of collagen cross-linking. In contradistinction, Dahners et al. [70] had shown an initial decrease in strength of an injured medial collateral ligament in the rat's knee with piroxicam treatment. However, this was followed by an increase in strength several days later. This change has been attributed to an increase in collagen synthesis. This resulted in increased mechanical strength during healing, but there was no demonstrated further effect after completed healing.

The deleterious effects of either deliberate or inadvertent injection of dense connective soft tissue, such as ligament or tendon, has long been a concern in sports therapy [71]. Noyes and associates [72–73] provided an authoritative review of the local effect of methylprednisolone acetate injection into the anterior cruciate ligaments of rhesus monkeys. The two protocols called for an intracollagenous injection or two infra-articular injections in the knees. They found that alterations in ligament behavior depended on the dosage and the time after injection, with larger doses, a significant decrease in maximum load tolerance was noted; maximum load declined 27% at 15 weeks in one study group and remained at this level at 1 year [73]. In a large-dose group of animals, decreases in energy to failure were minimal at 6 weeks but showed a 43% decline at 15 weeks. It was concluded that "a single intra-ligamentous or multiple intra-articular steroid injection has the potential to cause significant and long-lasting deterioration in the mechanical properties of ligaments and collagenous tissues [73]." Attention was called to fibrocyte death within the ligament adjacent to the injection site and the delay of the reappearance of viable fibrocytes for as long as 15 weeks [73]. In a follow-up study, three intra-articular injections of methylprednisolone acetate were given at 1-week intervals to the knee joints of rhesus monkeys [73]. In load-failure studies of bone-ligament-bone preparations, time-dependent and dose-related changes in mechanical properties were noted. Weakening of mechanical properties was significant in the large-dose group, which received the equivalent of 10 times the normal human dose (based on body mass calculation) but was insignificant in the small-dose group when they received approximately the equivalent of a normal human dosage, as a single intra-articular injection or repeated injections, several months apart [73]. Kennedy and Willis [74], studying rabbit Achilles tendons treated with betamethasone sodium acetate, administered 25 to 50 of the usual adult

dosage and then killed the animals at five intervals between 48 hours and 6 weeks. They were able to correlate failure at a loading rate of 12.5 cm/min with underlying histologic changes, large cystic spaces and collagen necrosis appeared as early as 48 hours. It is not clear whether these changes were the result of pressure necrosis or secondary to the fluid volume, the toxic effects of injection, paraben preservatives, and known coincident chemicals present in the steroid preparation, or to a steroid catabolic effect. Neutrophils and macrophages were present as early as 7 days in a typical acute inflammatory and vascular response to wounding; their appearance was followed by the gradual development of acellular, amorphous precursors of collagen. Failing strengths at 48 hours were 35% lower than in controls, and then progressively improved until failing strength returned to normal at 14 days.

Electron micrographs demonstrated a partial return to the integrity of collagen fibrils at this stage, and more complete restoration at 6 weeks (see Figure 22-5A–D). Although it was not determined whether the observed weakening was a function of the steroid itself, of the induced inflammatory process, or both, the authors recommended avoiding vigorous muscular activity for at least 2 weeks after injection [74]. Repetitive local injection is also discouraged by these findings. One mechanism by which corticosteroids inhibit connective tissue formation is by preventing ground substance precursors of collagen from being sulfated [44]. Because 70% to 80% of the dry weight of ligament is collagen, it is assumed that steroids would inhibit tendon and ligamentous healing [65]. Recent work by Wiggins and Fadale [65] in acutely injured rabbit ligament model has demonstrated that injected ligaments possess the same tensile strength as non treated ligaments, but that they failed under lighter loads, possibly because of diminished cross-sectional area and histologic immaturity [5,71,72]. Because these findings can be repeated, despite delaying the steroid injection 7 days after injury, a detrimental mechanism of steroid action in addition to the inflammatory healing-repair phase may be present [65,66].

Problems such as modeling, species variation, dosage, and loading measure have led investigators to differ in their conclusions concerning the effects of injected corticosteroids on tendon. Matthews and associates [75], using a rabbit patellar tendon model, injected methylprednisolone acetate (3 to 4 4-mg doses, 1 week apart) and found no change in biomechanical properties, maximum load supported, stiffness, and mode of failure. However, the longest point of observation was 57 days, with an average of 33 days to the animal's death. They concluded that underlying degenerative abnormalities may contribute more significantly to tendon rupture after injection. Other studies have documented decreased fibrogenesis in cortisone-treated animals; decreased tendon weight, load to failure, and energy to failure; and a lower modulus of elastic stiffness [61,66].

In summary, despite the lack of appropriate animal models for overuse injury treatment study, the preponderance of present research has established that the most reliable effect of anti-inflammatory therapeutic medication is seen in the presence of excessive synovial inflammatory activity. The potential harmful effects on healing in tendon and ligament take on more clinical significance if one assumes that previously injured or diseased tissue is more vulnerable to an injection insult.

Clinical Precedent for the Use of Anti-Inflammatory Medication

The most commonly used NSAIDs are the salicylates originally derived from willow bark. The active ingredient, salicin, is converted to salicylic acid *in vivo* [37]. As such, this group of drugs forms one of the oldest therapeutics known to man. Current NSAIDs represent a heterogeneous family of drugs, all of which are analgesic, antipruritic and anti-inflammatory in activity. More recently, COX-2 selective anti-inflammatories have been added to this family.

Today, anti-inflammatory medications are the most widely prescribed therapeutic drugs in medicine. In 1984, it was estimated that nearly 1 in 7 Americans was treated with NSAIDs, and in 1986, 100 million prescriptions were written for these drugs [1]. In more recent studies that trend continued. Excluding over-the-counter use of ibuprofen, 8% of the population in the United States is exposed to NSAIDs; 75% of these prescriptions are for patients older than 65 years [1,6]. Virtually every ache and pain syndrome, as well as a vast variety of pathologic conditions including overuse syndromes, compression peripheral neuropathies, arthritides, tendinopathy conditions, synovitis, and tenosynovitis are thought to benefit from anti-inflammatory treatment [14].

In tendon injury, this widespread enthusiasm for anti-inflammatory therapy must be counterbalanced by the relative lack of evidence-based support. In a meta-analysis review of 185 articles published since 1966 on the treatment of lateral epicondylitis of the elbow, LaBelle et al. [15] found that only 19 of these studies were randomized and controlled. When these papers were rated for scientific validity, the mean score was only 33% with a minimum of 70% required for acceptance as a valid clinical trial. It was therefore concluded that scientific evidence was insufficient to support any of the current methods of treatment, including corticosteroid injection and NSAIDs. Weiler has provided another excellent

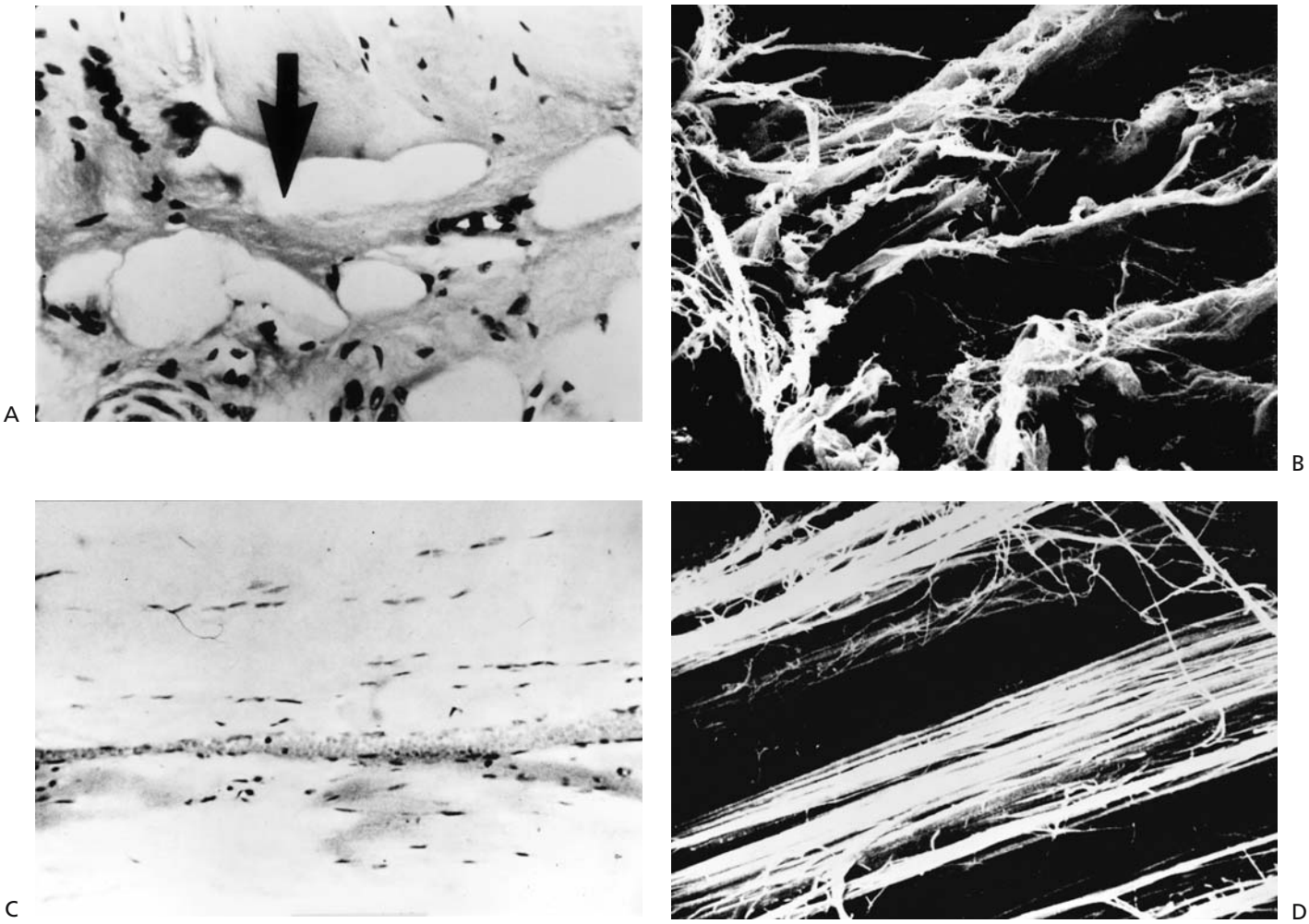

FIGURE 22-5. A, Light micrograph (x40) of steriod injected tendon (0.25 mL) showing early collagen necrosis and histologic disorganization 48 hours postinjection. B, Scanning electron microscopic view of injected tendon 48 hours after injection. Disorganization of collagen fibers is readily apparent (2750x). (From Kennedy JC, Willis RB. (1996) The effects of local steroid injection on tendons: a biomechanical and microscopic correlative study. *Am J Sports Med.* 4(1):11–21, with permission.) C, Light micrograph (40x) of tendon 6 weeks following injection. Note continued appearance of hyaline material at periphery. (From Kennedy JC, Willis RB. (1976) The effects of local steroid injection on tendons: a biomechanical and microscopic correlative study. *Am J Sports Med*. 4(1):11–21, with permission.) D, Scanning micrograph (1100x) of tendon 6 weeks after injection. Restoration of normal parallel collagen fibril arrangement is demonstrated. (From Kennedy JC, Willis RB. (1976) The effects of local steroid injections on tendons: a biomechanical and microscopic correlative study. *Am J Sports Med.* 4(1):11–21, with permission.)

meta-analysis with respect to the use of NSAIDs in sports or soft tissue injury, and found of 44 studies only 11 reports (20%) qualified as double-blind, randomized, and placebo controlled [14]. Of these, 8 reported positive results and 3 reported negative results, It was concluded that in the short-term studies, NSAIDs did not seriously delay the healing process when given soon after injury, Most benefits were often seen in treated patients compared to placebo-treated patients; the symptoms of injury, disability, and inflammation were slightly decreased in the treated patients. Overall, NSAIDs could neither be condemned nor strongly recommended.

Almekinders et al. performed a literature search from 1966 to 1996 of prospective studies on anti-inflammatory therapy of tendinopathy that were randomized, contained a control group and had an objective outcome variable [76]. A true meta-analysis was not possible because of the large variability and inclusion criteria, medication used, and follow-up. In the use of NSAIDs in chronic tendon injuries, 5 of 9 studies showed improved pain scores at final follow-up in the patients using NSAIDs. However, the maximum follow-up in these studies ranged from 7 to 28 days.

Corticosteroid treatment results revealed that 5 of 8 studies failed to show a clear difference at follow-up com-

pared with placebo or oral NSAIDs. However, short-term improvements were more significant with steroids, but recurrences were common [76]. Furthermore, LaBelle noted that no information could be found to document the natural course of the condition (e.g. lateral epicondylitis) [l5].

Thus, because many soft tissue injuries tend to improve with time, in those studies in which subjects were followed for a longer period of time, no lasting benefit was found compared with the placebo group. Improvements most often observed were seen as an early decrease in pain, improved motion, and early return to activity [14]. Nevertheless, it is hard to find any author who does not prescribe NSAIDs at some point in the management of tendinopathy.

This is particularly true with respect to shoulder complaints where typical endorsements include "nonsteroidal anti-inflammatory medication is started early [77]." NSAIDs, which are prescribed during the acute phase of pain, are "limited to a short course of 2 to 3 weeks and carefully monitored for production of side effects [77]," and "oral anti-inflammatory agents are effective and the author frequently gives a 3- to 4-week course of oral anti-inflammatory medication that can be used as necessary should symptoms return [78–80]."

There is some credibility to claims that NSAIDs administered in topical gels may produce a significant symptomatic effect. Thorling et al. compared Naprosyn gel with placebo gel in a double-blind, randomized trial in 120 patients with soft tissue injuries, mostly synovitis and tendinopathy, which had occurred within 48 hours of treatment. While symptom relief was comparable in both groups, the Naprosyn-treated patients improved more rapidly. Interestingly, physician evaluations of patient response did not differ statistically or significantly, whereas patients' subjective evaluations significantly favored the Naprosyn gel treatment [81].

Corticosteroid injection has become widespread in clinical practice, particularly with respect to upper extremity tendinopathy and bursitic conditions [82–89]. Hill et al., in a survey on the use of corticosteroid injection by orthopedists, found that 93% would inject a painful elbow epicondyle and 91% a shoulder bursa, the two most prevalent indications [90]. Bruno and Clark surveyed 52 orthopedic surgeons in the greater Cincinnati area and found the 4 most common sites of injection to be the subacromial arch, lateral epicondyle, finger flexor tendon, and the first dorsal extensor compartment of the wrist [91]. Of the responders, 100% thought that corticosteroid injection was effective in subacromial pain, 98% in lateral epicondilopathy, 94% in acromioclavicular joint pain, and 92% in de Quervain's syndrome. However, Stahl et al. reported only short-term benefits from injection of corticosteroid for medial epicondilopathy in a prospective randomized double-blind study, which revealed no difference in pain at 3 months and 1 year after treatment [92].

Furthermore, most authors decry repeated injection beyond 2 or 3, and point to the necessity to consider alternative treatment or surgery in such cases [78,93]. Support for this conclusion comes from a retrospective study by Bowen et al. of lateral epicondylitis, in which patients who achieved pain control after one corticosteroid injection successfully avoided surgery 88% of the time, whereas those requiring multiple injections avoided surgery only 44% of the time. The authors cautioned that "patients requiring multiple corticosteroid injections to alleviate acute pain have a guarded prognosis for continued nonoperative management [94]." In contradistinction, paratenonitis can be very responsive to corticosteroid injection. Gunther et al., in a series of 71 patients with trigger thumbs and fingers, reported that 90 of 104 objected digits (87%) remained asymptomatic for the duration of the study after only one injection (average follow-up 42 months). Each injection consisted of 0.6 mL of triamcinolone [95]. Kraemer et al., in a study of 253 consecutive digits with stenosing flexor tenosynovitis, recommended up to 3 injections with 20 mg of triamcinolone into the digital flexor sheath as initial management for a nonlocking stenosing flexor tenosynovitis, with an overall success rate of 68% without recurrence [96]. Response rates of 90% to 100% have been reported for injection therapy of de Quervain's tenosynovitis with the vast majority responding to a single injection [97,98]. With respect to the lower extremity, Schrier et al., in a literature review of Achilles tendinitis injection treatment, found only one randomized study with human subjects [99]. In an active population in which more than 70 were running more than 3 miles a day, corticosteroid injections neither improved the cure rate nor shortened the time to recovery. The patients receiving peritendinous corticosteroids had no significant improved outcome over the control group receiving only local anesthetic into the peritendinous tissues. The only other study Schrier found evaluated retrospectively the use of corticosteroids in the treatment of Achilles tendinopathy in a cohort of 83 patients [99]. Measuring recurrence as an outcome, 43% of the injection group suffered a recurrence whereas the noncorticosteroid group had only a 16% recurrence rate. Confounding these results were the differences between the corticosteroid and noncorticosteroid group. Generally those receiving corticosteroids tended to have more severe and more chronic symptoms [100].

A Clinical Rationale for the Proper Use of Inflammatory Medication in Tendinopathy

The clinician is often caught in a dilemma when considering the prescription of anti-inflammatory medication. Short-term gains must be weighed against potential costs and side effects, symptomatic relief versus complete func-

tional recovery, and the urgency of the patient versus the long-term risk of reinjury. In the author's experience, clinical utilization is often driven by the need to satisfy the expectation of the patient. Although many patients are fearful of "needle" therapy, many have come to anticipate the quick fix and pain relief of such treatment.

When first encountering the symptomatic patient, one must ask 4 basic questions: 1) Is the problem serious? 2) Will continued activity cause harm? 3) How can the patient best be rid of the problem? and 4) When can normal activity resume? In the context of this agenda, the clinician immediately faces the dilemma of defining the character and extent of the tissue injury. Although this may be less problematic in acute injury, it is typically difficult in chronic injury because the time of onset, contributing factors, severity, exact anatomic nature, and classic signs of inflammation after injury are not always present or identifiable. The complaint is not so much identified with specific structure as within an anatomic area. It is a "painful shoulder," not a painful rotator cuff that the patient describes. The onus on the examiner is to be confident in making an accurate physical diagnosis, but the elicitation of pain does not necessarily shed light on the exact pathologic condition of the tissue or the mechanism of injury. The history becomes paramount in determining the staging of such complaints. A considerable amount of experience may be required to detect contributing causes of disability, such as subtle muscular insufficiencies or occult joint pathologic laxities (see Figure 22-6).

Rovere's attempt to define tendinopathy in the study of theatrical dance students exemplifies this difficulty. He defined tendinopathy as "a syndrome of pain and tenderness localized over a tendon, usually aggravated by activities that bring the particular muscle-tendon unit into play, usually against resistance . . . the syndrome is inclusive of tenosynovitis and tenovaginitis as well as actual inflammation of the tendon substance itself [101]." The distinction of acute and chronic injury is probably somewhat artificial. The patient may present with either inflammatory-dominant or tissue-degenerative dominant forms at the site injury. For instance, in the shoulder, a subacromial inflammation secondary to impingement may evolve to include a diagnosis of rotator cuff tear; degenerative disease of the shoulder soft tissue, such as the rotator cuff, is more prevalent with age [102]. Although plain radiographs may show dystrophic soft tissue calcification as a clue to such existing tissue degeneration [103], this does not always imply a failed clinical outcome to anti-inflammatory therapy. However, recurrence of symptoms is more likely. Such findings often form the nidus of a chemical irritant, especially in the supraspinatus tendon with sensitive adjacent subacromial bursal tissue. Anti-inflammatory injections may be followed by spontaneous resolution of dystrophic calcium deposits in both the shoulder and elbow (see Figure 22-7). Both bone scans and MRI imaging have added increased accuracy to assessing tissue damage extent, but the finding of such damage does not preclude a response to anti-inflammatory treatment. Contrarily, a positive bone scan may be useful in further justifying an attempt at injection therapy by verifying the presence of a potential inflammatory response (e.g. at a tendon enthesis). However, no present form of soft tissue imaging, as a single point of observation, is reliable in assessing time of onset, duration or eventual rate of resolution when first encountering a given complaint.

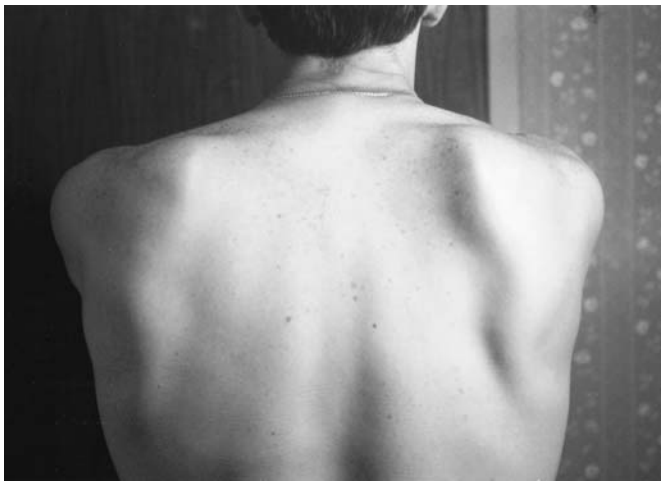

FIGURE 22-6. Scapular dyskinesis (winging), right shoulder, due to overuse-induced fatigue. Attempts to treat accompanying rotator cuff tendinopathy must address dynamic stabilization upon the shoulder kinetic chain for which anti-inflammatory symptom relief is not a solution.

The key steps in the management of all soft tissue injury are:

1. To establish an accurate and complete diagnosis of all the anatomic and dysfunctional components of the injury.
2. To minimize the deleterious local effects of the injury by controlling excessive inflammation and secondary tissue damage.
3. To allow progressive anatomic healing of the injury.
4. To maintain other components of fitness.
5. To regain previous functional status.

Both acute and chronic forms of injury may have an inflammatory component; however, not all pain is inflammatory (see Figure 22-8). The more chronic the injury, the more likely that permanent structural damage has been acquired that may be unresponsive to medication alone. The efficacy of medical modifiers of inflammation depends in large part on where in the spectrum of tissue injury between inflammatory-dominant and degenerative-dominant states the particular injury lies (see Figure

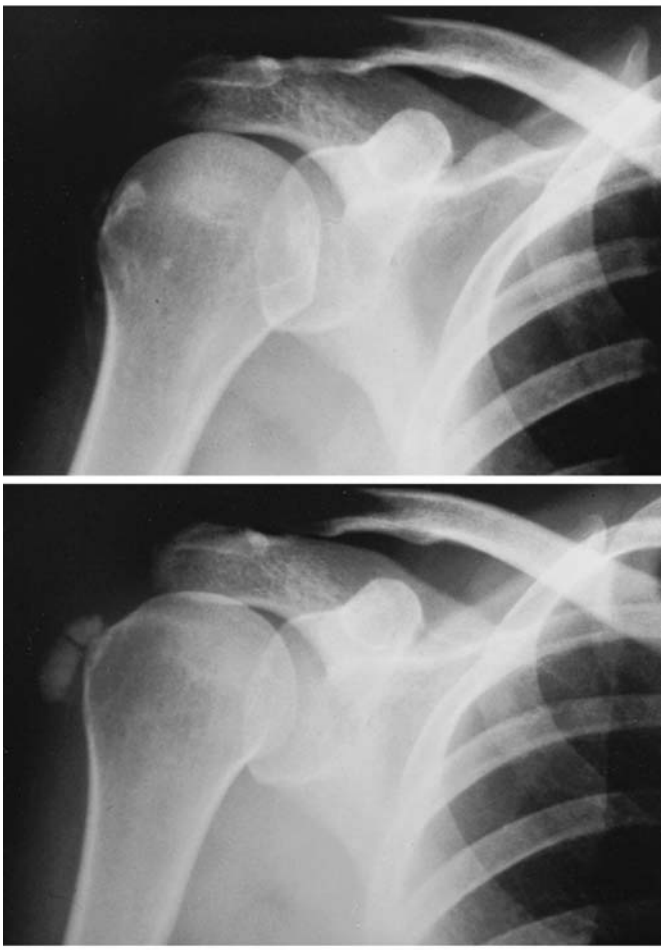

FIGURE 22-7. A, Dystrophic calcification, rotator cuff: Pretreatment radiograph appearance. B, Same patient, 3 months post-treatment. Radiograph reveals deposit to be nearly fully resorbed after needing with barbitage technique (i.e., multiple penetrations of tendon and forceful aspiration). Corticosteroids are instilled in adjacent subacromial bursa only. Although resorption may result from increased vascular response to local wounding or local chemical effects, the exact mechanism is not well understood.

22-9). Only through an accurate history, physical diagnosis, and trial of therapy can the correct therapeutic plan be defined for an individual patient. Anti-inflammatory medication is prescribed for relief of disabling pain and inflammation in acute injury, but with little pretense that it will be the sole solution. Likewise, the initial objective in the treatment of chronic overuse injury should be to recognize the problem in the greater context of the underlying promoting cause (e.g. abusive training, occult joint instability, transitional overload), not solely to suppress symptoms. I often summarize this approach in the mnemonic **RESTM: R**est and **R**ehabilitation, **E**ducation and **E**ccentric exercise, **S**upport of the injured part, **T**raining and **T**echnique improvement, **M**odification of activity, and **M**odalities and **M**edication. Because no drug can speed time-dependent healing processes, anti-inflammatory therapy remains an important adjunct to a comprehensive treatment program that includes: 1) protection of the early phases of tissue healing while normalizing as much as possible all remaining limb function; 2) avoidance of excessive immobilization; 3) Restoration of total limb function by emphasizing the timely application of therapeutic and rehabilitation techniques; 4) reconditioning; and 5) elimination of the abusive behavior [104].

Historically, the popularity and enthusiasm for the clinical application for NSAIDs and corticosteroid injection have largely been driven by the experience with rheumatologic diagnoses. These intrinsically autoinflammatory diseases seem to share some aspects of pathobiology with traumatic-onset degenerative complaints and inflammations associated with tendinopathy, especially in synovial systems where corticosteroid-induced "chemical synovectomy" is still a highly regarded benefit. As previously noted, increasing evidence now suggests that autoimmune mechanisms may be also triggered and responsible for the inappropriate persistence or intensity of chronic inflammation in paratendinopathy.

Inability to cooperate with a total rehabilitation protocol, combined with activities of daily living and/or night pain, favors the consideration of injection therapy [105]. The best indication for steroid injection remains a localized inflammatory site, such as a synovial cavity, bursa, tendon, synovial sheath, or granulation tissue. Factors contributing to a lack of response to injection therapy are inadequate injection technique and failure to prescribe a comprehensive rehabilitation program, (see Table 22-1). Successful medical treatment depends on the favorable combination of three factors: 1) proper prescription and timing of the medication; 2) the severity of the injury; and 3) the potential for the host tissue to generate a reparative response (see Figure 22-10). The importance of rest after injection has been emphasized both for structural recovery of adverse tissue effects as well as inflammation resolution [65,71]. Criteria for return to activity should include some form of grading or staging to allow for progressive moderations of activity [2].

Because surgical options are often considered after a trial of nonoperative care that includes appropriately prescribed anti-inflammatory medication, corticosteroid injection should not be the first treatment alternative, nor should it be the last used in aiding the patient. Because the long-term risk of side effects and cumulative tissue damage from anti-inflammatory treatment has been well documented, the clinician should have a firm idea of when such treatment is no longer likely to be effective. Surgical treatment may be indicated if there is failure to progress in a well-designed, comprehensive rehabilitation program, for usually 3 to 6 months, and other conditions exist such as altered quality of life, constant pain without activity including night pain, objective evidence of refrac-

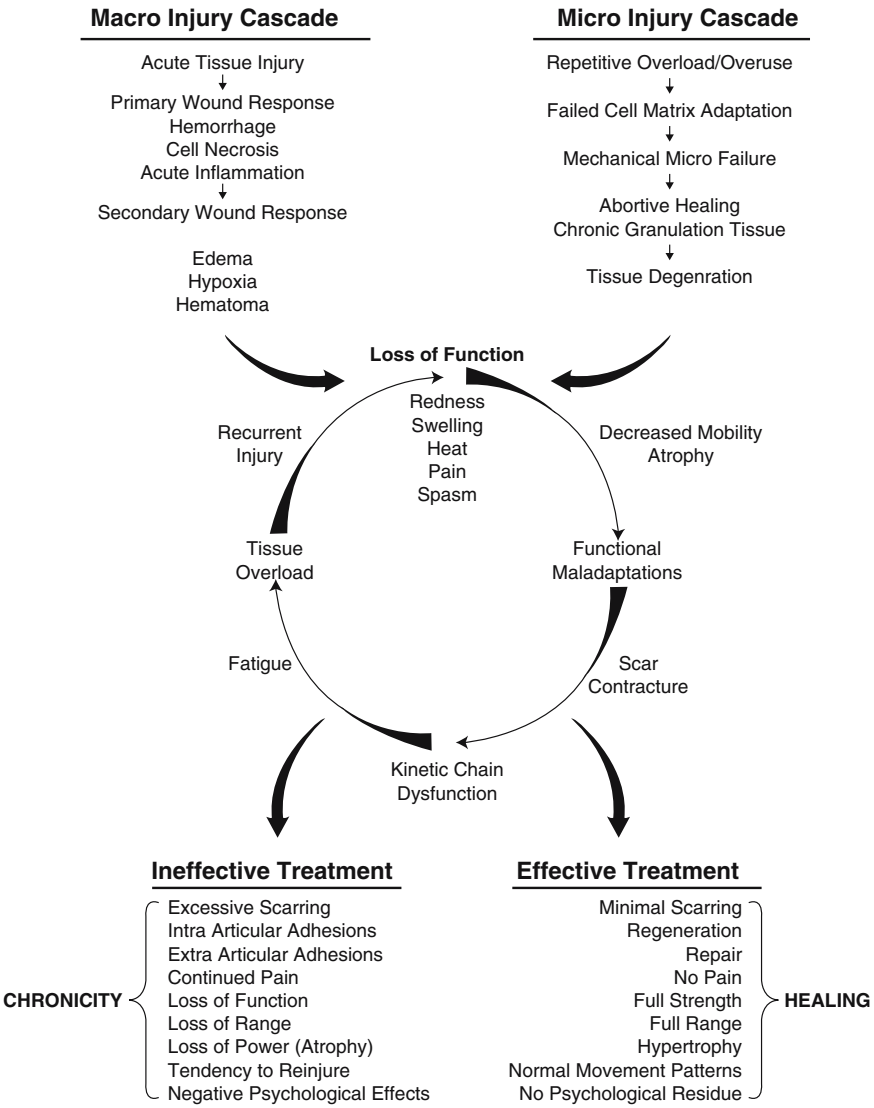

FIGURE 22-8. Injury-inflammatory cycle. Effective treatment is multifactorial. (From Leadbetter WB. (1994) Soft tissue athletic injury. In: Fu FH, Stone DA, eds. *Sports Injuries: Mechanisms-Prevention-Treatment.* Baltimore: Williams and Wilkins, p. 765, with permission.)

TABLE 22-1. Factors contributing to lack of response to injection therapy

Athlete related
Persistent overuse
Intrinsic factors (e.g., age, genetics)
Faulty technique
Evidence of advanced disease (e.g., calcification on radiograph, positive MRI, degenerative joint disease)
Physician related
Improper diagnosis
Inadequate injection technique
Failure to provide a comprehensive rehabilitation program

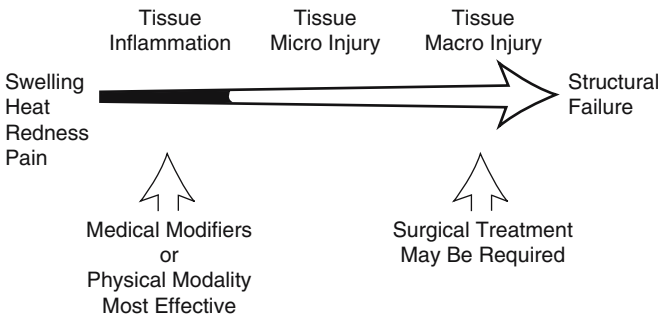

FIGURE 22-9. Spectrum of soft tissue injury pathology. Medical modifiers are most effective prior to structural failure.

tory tissue injury (plain radiography, arthrography, MRI, sonography), persistent weakness, atrophy or limb dysfunction, or an unwillingness to modify or give up our activity [104]. However, too often the term "conservative" is used to connote a safer, less radical, and generally nonsurgical treatment. This conception is flawed if the word "conservative" is used to sanction an oral medication that produces a serious systemic side effect or to administer multiple corticosteroid injections despite lack of improvement. The prescription of a nonsteroidal drug in the face of stomach pain should not be considered conservative, any more than operative treatment of a ruptured appendix should be considered radical. The clinician should strive to maintain a perspective on a spectrum of available therapeutic modalities within a range of nonoperative and operative choices. Generally, oral anti-inflammatory medication and rehabilitation will precede considerations of local injection, which in turn precedes surgical considerations. In any given individual, care should be taken not to prolong ineffective anti-inflammatory symptomatic treatment, thereby deferring a more effective surgical remedy and denying the patient the long-term benefit of structural restoration and improved limb function. Principles for proper application of corticosteroid infection therapy are summarized in Table 22-2.

Practical Concerns in Prescribing Anti-Inflammatory Medication

The successful prescription or application of anti-inflammatory medical treatment is as much an art as science, experience as formula. Getting started in the face of the plethora of commercially available and intensely marketed NSAIDs and corticosteroid preparations often leaves the inexperienced clinician either ambivalent or committed to rote habit. A sense of indifference is underscored by statements such as that of Leach and Miller, who noted: "We have not found any one particular nonsteroidal anti-inflammatory agent to be significantly more efficacious than another, and the choice should be left to the treating physician's discretion [107]." Such statements should not be construed to imply that the prescription of nonsteroidal anti-inflammatory medication is taken lightly or that changes in medication may not impact on patient response.

Similarly, a prominent reason for failed anti-inflammatory injection therapy is improper application predicated on a poorly defined objective and an inability to selectively medicate the target tissue while avoiding normal anatomic structures. To overcome these concerns, it is helpful to draw attention to established guidelines in the literature.

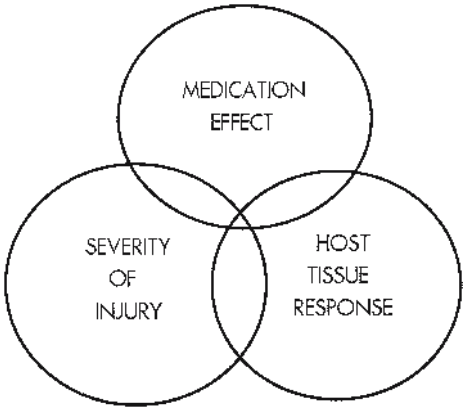

FIGURE 22-10. Factors for successful treatment of athletic injury.

TABLE 22-2. Use and abuse of corticosteroid injection

Effective use
Six-week preinjection trial of rest, adjusted level of play, and conditioning
Discrete, palpable site of complaint (avoid tendon)
Peritendinous or inflammatory target tissue
Limit of three injections, spaced weeks apart, given only if first led to demonstrated improvement
Rest (protected activity) for 2 to 6 weeks after injection
Correct contributing mechanical cause of injury (e.g., improper equipment, overtraining, improper technique)
Ineffective use
Acute trauma
Intratendinous injection
Coincident infection
Multiple injections (>3) despite lack of response
Injection immediately before competition
Frequent intra-articular injections in lieu of a defined diagnosis
Joint instability or malignment
Charcot joint

NSAIDs

NSAID efficacy is very sensitive to host interaction [108]. The pharmaceutic parameters of these drugs depend on their absorption and bioavailability, their distribution throughout the body, and their half-life. There is considerable variation in peak dosing, based on half-life, with short-acting preparations, such as acetylsalicylic acid being 0.2 hour, whereas long-acting preparations, such piroxicam, have half-lives of 35 to 50 hours. Because steady-state plasma concentrations are achieved after a period of dosing extending for 3–5 half-lives, NSAIDs with longer half-lives may take several days to achieve maximal clinical effects [87]. When first prescribing these drugs, no one agent is demonstrably superior to another in a given individual, and the choice must, therefore, be made on the basis of convenience of administration, toxicity profile, and previous experience of the patient.

Patient compliance is significantly better with drugs that require once- or twice-a-day dosing [108]. Shorter-lived preparations may be more useful in acute pain, as opposed to longer-lived agents in chronic conditions. Despite some conflicting evidence, there is roughly a linear relationship between the plasma concentration of NSAIDs and observed clinical response and toxicity. Because of the variability of half-life as well as marked variation in individual patient responses to NSAIDs, it is important to be familiar with the chemical classification of these drugs.

When encountering variability in clinical response and sensitivity to side effects, selecting an alternative drug is useful. Availability of COX-2 inhibitors provides greater margin of safety, but, to date, no studies have shown greater efficacy in tendinopathy. Clearance of NSAIDs is predominantly by hepatic metabolism, with inactive metabolites being excreted in the urine [82]. Clearance of some NSAIDs, including difusinol (Dolobid), ketarogis, fenoprofen (Nalfon), naproxen (Naprosyn), and indomethacin (Indocin) is decreased in renal failure. In addition to liver and kidney disease, old age has a significant adverse influence on toxicity and susceptibility to nonsteroidal medication. With increased age, serum albumin concentration has been noted to decrease from a mean of 3.9 to 3.0 g/dL. Salicylate binding was noted to decrease from 92% in the young to 79% in the elderly, at total salicylate concentrations of 140 mg/L [40]. Thus, an increased unbound salicylate fraction can result in increased toxicity in the elderly [40]. Drug distribution is altered by decreased total body water and lean body mass and increased body fat in the elderly. Changes in drug receptors occur, also, with aging [10,108]. All of these findings enhance the possibility of adverse reactions in the elderly.

When prescribing NSAIDs, initial prescription should be limited to a maximum of 14 days. Any longer prescription should be accompanied by careful monitoring. Most authors recommend stopping such medication to assess the clinical benefit and renewing such a prescription only under clinical observation [13]. NSAIDs often exhibit major interactions with other medications often taken by the elderly. Common adverse drug interactions include interference with diuretics and hypertensive drugs, oral hypoglycemic drugs, anti-coagulants and renal metabolized medications [8]. Clinical guidelines for the prescription of NSAIDs are summarized in Table 22-3.

Table 22-3. Guidelines for NSAID prescription

Clinically useful
Reduction of synovitis—joint, bursa, tendon sheath
Adjunctive pain relief of acute and chronic injury
Postoperative pain control
During a comprehensive rehabilitation program
Cautions
Beware in the elderly
Avoid use in minor conditions
Do not prescribe for "at risk" patient, especially the triad syndrome: nasal polyps, asthma, aspirin intolerance
Consider alternative (e.g., topical agent, acetaminophen)
Consider use with protective drugs (i.e., H_2 antagonists)
Monitor patients regularly (CBC, hepatitic, renal assessment)
Do not give in first trimester of pregnancy
Beware of previous adverse history to drug
Keep use to a minimum

Corticosteroid Injections

Keys to successful corticosteroid injection therapy can be briefly summarized as where to inject, how to inject, what to inject, and when to inject.

A first step is to select the proper corticosteroid medication. Injectable corticosteroids vary primarily in duration of action and solubility [59]. The experienced clinician will become familiar with at least one soluble short-acting preparation and one long-acting insoluble preparator, as their applications differ. I prefer plain betamethasone sodium phosphate (Celestone) for use in paratendon injection, as there is almost no risk of crystalline precipitate. Triamcinolone hexacetonide (Aristospan) is one of the least soluble corticosteroid esters and is, therefore, an excellent choice for achieving long-term effects in bursae [53]. I personally avoid depo preparations in soft tissue injection because of observed adverse steroid deposition. In addition, methylprednisolone acetate (Depo-Medrol) is typical of most bottled corticosteroid preparations in that the solution contains several other active ingredients as well. Typical contents include such compounds as polyethylene-glycol 3350, sodium chloride, hydrochloric acid, phenol, and myristyl picotinium chloride, whereas the multiple-dose vial has an additional ingredient, benzyl alcohol. Betamethasone sodium phosphate preparations contain sodium bisulfate in addition to phenol. Sodium bisulfate is thought to be responsible for the potential anaphylactic reactions to corticosteroid injection seen in some sensitive patients. Phenol is a recognized caustic agent in soft tissues. The potential adverse tissue effect of these types of chemicals, when inadvertently injected into dense connective tissue, has not been well documented but, I believe, represents a potential source for observed intratendinous degenerative side effects.

It is common practice to add Xylocaine and corticosteroid agents together in the same syringe, which allows for better distribution of the medication in the soft tissues and an immediate analgesic effect to accompany the injection. This is the basis for the diagnostic "pain ablation test." It should be noted that advice given in the product circular cautions against this practice because of flocculation of the agent, commonly seen with most methylparaben-preserved injectable analgesics including Xylocaine, lidocaine, and Marcaine. The potential adverse effect of this flocculation is controversial. Some experienced clinicians express little concern despite the manufacturer's cautions on diminishment of efficacy,

presumably because of changes in solubility and drug distribution [58]. Although all of these observations require further study, the knowledgeable clinician should strive to establish a consistent pattern in his practice. Xylocaine is obtainable in single-dose vials that are methylparaben free (Xylocaine-MPF) (see Figure 22-11).

During actual injection, sterile gloves are advisable for personal safety. Aseptic technique is mandatory. Careful preparation of the skin should not be overlooked. This is especially a concern in areas where there is likely to be surface contamination embedded into the skin, such as in palm of the hand. A mini surgical scrub with Betadine solution or chlorhexidine may be appropriate. A Betadine swab applied to the exact point of the injection helps both to focus the clinician's point of insertion at the maximum point of tenderness as well as to prepare the skin. Additional swabbing with alcohol immediately before skin penetration is recommended. Needle size varies with the joint or structure involved. I prefer a 21-gauge, 0.5-inch needle for subacromial bursal injection and usually otherwise prefer a 25-gauge, 0.5-inch needle for other applications in the upper extremity, especially injection of paratenonitis associated with trigger finger or de Quervain's. Because a small-bore needle discourages aspiration, a larger-bore needle is used to draw up the medication, and then a switch to the appropriate therapeutic needle is made. This also adds an additional preventive measure for any inadvertent contamination during aspiration. Because there is a potential risk of infection complication from injection, I prefer to draw up my own medications to be absolutely certain that there is no break in sterile technique.

Attention should be paid to positioning the patient prior to injection. Sensitive or anxious patients may not be safe in a sitting position and should be supine, to avoid inadvertent injury due to a syncopal reaction. In all cases, the patient, at a minimum, is maintained sitting on the examining table such that a supine position can be assumed in an emergency. The sitting position for subacromial injection is preferred, as there is gravity distraction of the subacromial space. Gentle traction by an assistant or with the clinician's free hand can also create this effect or augment it in the sitting or the supine position. It is helpful to maintain a confident and reassuring attitude and to explain carefully the purpose and the sequence of events that the patient is to experience.

Local infiltration of the skin with an anesthetic or a topical spray anesthetic preparator can be a helpful adjunct but has not been routinely necessary. A gentle, continuous insertion and attention to finding the appropriate soft tissue spaces for deposition of the medication are important [88,106].

Because of the familiarity with posterior and lateral approaches to the subacromial space and glenohumeral space required with present-day arthroscopy of the shoulder, I prefer a slightly posterior approach to the subacromial bursa. I rarely will inject anteriorly because of the difficulty in avoiding the biceps tendon. Because I rarely make a diagnosis of biceps tendinopathy in the absence of subacromial symptoms, I prefer to inject the subacromial bursa as an initial trial of therapy with some expectation of diffusion providing an anti-inflammatory effect to the adjacent biceps tendon.

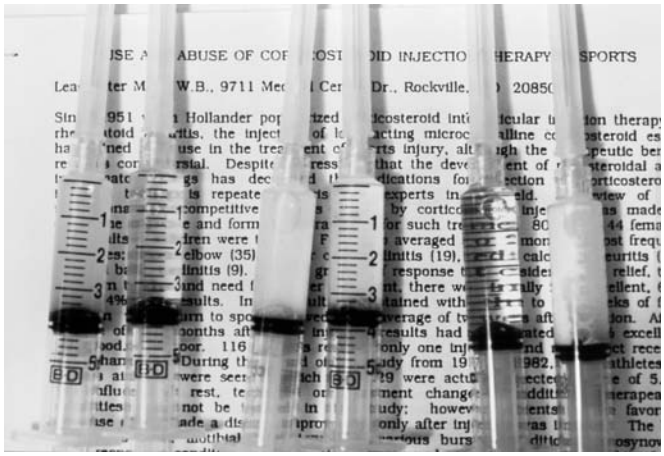

FIGURE 22-11. Miscibility of common injectable corticosteroids: Depending upon the choice of analgesic solvents, miscibility may vary greatly with the same corticosteroid.

In refractory cases, I prefer injecting posteriorly within the glenohumeral joint and allowing the intra-articular extension with the biceps tendon sheath to act as a conduit for bathing of the biceps tendon (see Figure 22-12).

Injection of the epicondyle for lateral epicondylar pain, paratendinitis, or tendinosis with chronic inflammatory reaction is best done with a direct approach to the point of maximal tenderness and with the needle directed to penetrate through the aponeurosis of the extensor mechanism (see Figure 22-13). This passage can be often detected with gentle approach, and the lack of resistance during the injection is an additional guide to avoiding intratendinous or ligamentous deposition. It is important to avoid overenthusiastic subcutaneous distribution and overinfiltration of the subcutaneous tissues—especially of the lateral elbow—to avoid subcutaneous atrophy as well as cutaneous depigmentation. This complication has also been reported in the shoulder.

The technique for injecting a tendon sheath has been refined by several authors [95,96]. I prefer to insert a 25-gauge or a 27-gauge needle (i.e. pulley) directly into the flexor tendon near the site of the stenosing tenosynovitis, and detach the syringe to observe displacement of the needle caused by the movement of the flexor tendon. The needle is then gently withdrawn until this motion no longer occurs, and this observation is used as a guide to maintain an intraparatenon injection without intratendinous introduction (see Figures 22-14, 22-15, and 22-16).

Goss and Adams have identified 4 principles in the clinical application of corticosteroid injection: 1) select

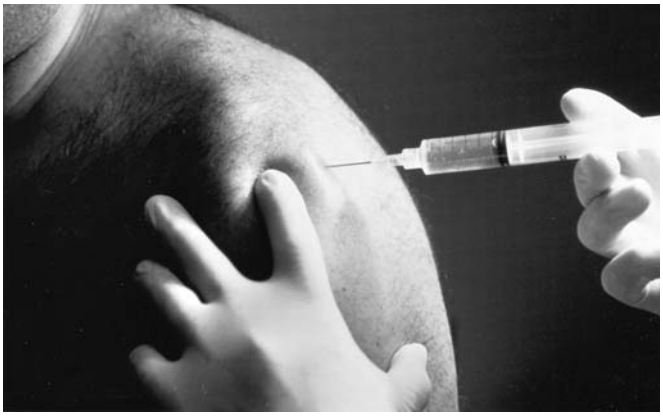

FIGURE 22-12. Proper injection technique, subacromial bursa. Note palpation of posterior "soft spot" on edge of acromion.

the smallest, most efficient needle necessary to accomplish the mission; 2) use the most appropriate route of entry, depending on whether a simple injection or arthrocentesis is planned; 3) choose the most appropriate corticosteroid; and 4) use a smooth and steady touch [109].

Adverse Effects of Anti-Inflammatory Medication

NSAIDs

All medications have side effects, and therefore the cost-benefit ratio of treatment must always be carefully considered. Ironically, although corticosteroid injection

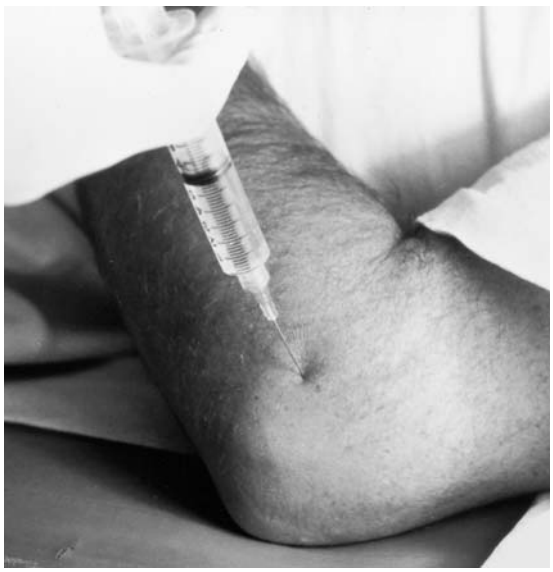

FIGURE 22-13. Proper injection technique, lateral epicondyle. Note direct insertion over extensor carpi radialis brevis tendon, "feel" for subaponeurotic space.

FIGURE 22-14. Proper injection technique, stenosing tenosynovitis of finger flexor tendon. Initial placement of 25-gauge needle near A pulley penetrates tendon.

FIGURE 22-15. Needle tip, depth of penetration confirmed by gentle active or passive motion of digit.

FIGURE 22-16. Note metronome-like excursion of needle when imbedded in tendon. The needle is then withdrawn until digital movement ceases to create motion of the needle hub. This point is also detected by a subtle crepitance transmitted through the needle as the free needle tip is brushed by the gliding tendon. Injection is then introduced guarding against tissue resistance and observing the inflation of the tendon sheath in the palm. (Technique courtesy of Leo M. Rosmaryn, MD. Washington Hand Center.)

therapy is often regarded by the patient as the more extreme measure, an oral NSAID can carry far greater systemic risk. In addition, the financial cost of maintaining patients on an oral anti-inflammatory medication is significant, in one report ranging from $10 to $178 US per month [6]. Owing to the relative nonselectiveness of prostaglandin isozyme suppression, traditional NSAIDs are another form of chemotherapy in which, ideally, the problem is cured slightly faster than a side effect is generated.

Concerns regarding the risks of nonsteroidal drugs are not new. Black et al. called attention to the use of phenylbutazone in sports medicine in 1980 [110]. It was noted that phenylbutazone had surpassed chloramphenicol as the most common cause of fatal drug-related aplastic anemia. At that time, phenylbutazone ("bute") was the most commonly prescribed drug in the National Football League, with an average of 24- to 40-unit doses per player per season. Such observation has subsequently resulted in phenylbutazone no longer being commonly prescribed. Trends that apply to present-day NSAIDs include a tendency for adverse reactions to present early in the course of treatment (84% of reactions occurred after the first week of treatment in one series); complications increased with age, with only 10% occurring in patients less than 40 years old, and 95% of fatalities occurring in patients over 40; and a significant increase in toxicity with increased dosage level [14].

Whereas present-day nonsteroidals are not as notorious as phenylbutazone, age greatly magnifies their risk [1,12,14]. NSAID use accounts for 70 000 hospitalizations and 7000 deaths per year, and the elderly population are at higher risk for adverse effects, including bleeding (7-fold increasing) [8]. One confounding factor in the elderly is that symptomatology does not parallel pathology, and bleeding can occur with only minimal antecedent symptomology [8]. Gastrointestinal toxicity is most common, occurring in up to 20% of patients on full doses of NSAIDs; peptic ulcer disease occurs in 1% to 2% who receive NSAIDs. There is concern that the syndrome of NSAID-associated gastropathy may be responsible for over 2500 deaths per year in patients with rheumatoid arthritis [6]. Padgett has noted particular risk factors for the development of nonsteroidal-associated peptic ulceration: age over 65 years, a past history of peptic ulceration, concomitant corticosteroid ingestion, and multiple organ dysfunction [111]. Patients with the "triad syndrome" (asthma, nasal polyps, and aspirin intolerance) may have fatal reactions after ingestion of NSAIDs and should not be treated with these drugs [14]. It has been estimated that 50% of patients receiving NSAIDs may have an adverse reaction of some kind, and that 1% to 2% of these reactions may be serious [111].

Because NSAIDs are metabolized through the liver and profoundly affect prostaglandin-driven renal functions, any coexisting liver disease such as chronic hepatitis or cirrhosis, or evidence of renal disease, is a relative contraindication to prescribing NSAIDs [6]. In assessing the drug risk in the elderly, it is important to remember that the older patient may have a normal serum creatinine, but a creatinine clearance that is markedly reduced [111].

The recommended ulcer prophylaxis for NSAID-induced ulcers is the prostaglandin analogue, misoprostol (Cytotec). Cytotec is the first drug that is specifically approved for this indication [111]. H2 blockers have not been shown to be effective in preventing NSAID-induced ulcers. These constraints provide an additional incentive for finding alternative treatment and for constantly justifying the persistence of treatment with NSAIDs.

Nonsteroidal drug intolerances in the elderly are not an irrelevant issue in today's aging demography. With 20% of the US population and one-fifth of the world's population estimated to be over the age of 65 by the year 2050, an increasing trend for longevity and fitness in the elderly can be expected to challenge the clinician to treat a great number of tendon injuries in the aging patient [8].

Corticosteroids

Both local and systemic complications of corticosteroid injection therapy have been described [71]. Local complications include subcutaneous atrophy or fat necrosis, depigmentation or hyperpigmentation, tendon or ligament rupture, accelerated joint destruction or osteolysis, and flare reactions. Systemic responses include significant transient hyperglycemia in diabetics, transient leukocytosis, vasovagal attack, psychological problems, and systemic allergic reaction [106].

A review of our own experience has been reported with 124 patients, 116 of whom received only one injection and none of whom received more than 4 injections in one site [106]. The complications included 4 cases of local skin depigmentation; 4 cases of intratendinous or intrabursal precipitates (documented at surgery); and one case of subcutaneous atrophy (see Figure 22-17). No tendons ruptured, probably because injections of the Achilles and biceps tendon sites were avoided. Bruno and Clark [91], in a survey of 52 practicing orthopedic surgeons, recorded the following percentages of various complications: fat necrosis 64% (most commonly at the elbow); skin depigmentation 67%; tendon rupture 17% (biceps 4%, Achilles 3%, patellar 1%); accelerated joint destruction 17% (knee, 7%); and systemic reactions 60% (hyperglycemia 10%; vasovagal reactions 15%). Hill et al. [90] reported the experience of 233 orthopedists and found the most frequent complication to be subcutaneous fat atrophy 65%; skin pigmentation changes 54%; and tendon rupture 39% (see Table 22-4). The effect of corticosteroid injection, especially if multiple sites are injected in one patient, upon the hypothalamic-pituitary-

adrenal axis has been well documented [63]. I have seen elevations in serum glucose of 200 to 300 dL after a single 40-mg triamcinolone hexacetonide injection. It is important to warn any diabetic patient of this transient side effect, which has not posed a problem if control medication is properly adjusted. Also, prominent leukemoid reactions with total white cell counts of 16000 to 20000 have been observed.

Spontaneous tendon rupture as a complication of corticosteroid injection has not undergone controlled study. Ford and DeBender [112] reported 15 ruptured tendons (8 biceps tendons, 3 Achilles tendons, 2 supraspinati, one anterior tibial tendon, and one lateral epicondylar attachment) in 13 patients. In most cases, triamcinolone acetonide mixed with procaine or lidocaine had been used. Kelly and associates [113], in a discussion of patellar and quadriceps tendon ruptures, noted that 8 knees had been injected with corticosteroids near the involved tendon at various times before rupture. Most patients had received an average of 2 to 3 injections; none had received more than 12. Four patients were professional basketball players, although it is not clear whether they were among the patients receiving injections. Kleinman and Gross [114] reported Achilles tendon ruptures in 3 patients within 6 weeks of their receiving a single local steroid injection each. On the basis of rounding of the tendon ends and preexisting degeneration changes at the time of surgical repair, they concluded that it was not likely that the ruptures reflected a mere progression of existing tendinopathy.

Table 22-4. Corticosteroid complications observed by 233 orthopedists

Complication	Number of Orthopedists (%)
Subcutaneous fat atrophy	150 (64)
Skin pigmentation changes	125 (54)
Tendon rupture	91 (39)
Cartilage damage	46 (20)
Infection	42 (18)
Foreign-body reaction	18 (8)
Sterile abscess	15 (6)
Peripheral nerve injury	14 (6)
Muscle damage	9 (4)
Anaphylaxis	5 (2)
Vascular injury	1 (0)

*Values are number of orthopedists who observed complication, with percentage in parentheses.
From Fadale PD, Wiggins ME: Corticosteroid injections: Their use and abuse. J Am Acad Orthop Surg 2:134, 1994; *adapted from* Hill JJ Jr, Trapp RG, Colliver JA: Survey on the use of corticosteroid injections by orthopaedists. Contemp Orthop 18:39–45, 1989; with permission.

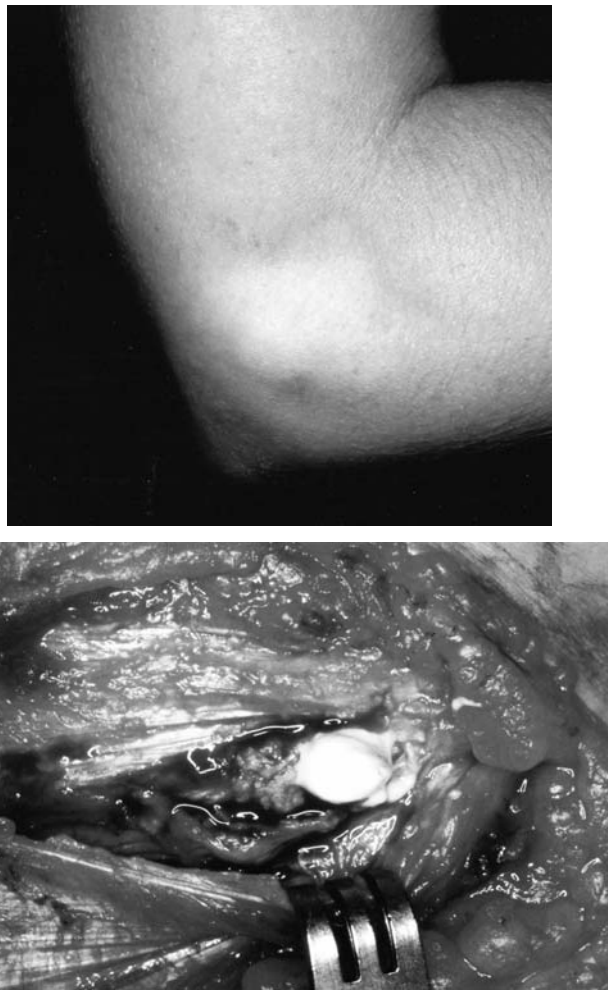

Figure 22-17. Complications of corticosteroid injection therapy included 4 cases of local skin depigmentation, 4 of intratendinous or intrabursal precipitates (documented at surgery), and one case of subcutaneous atrophy.

It is not clear why the degenerative changes were ascribed to the effects of injection rather than to other forms of microtrauma, and it also is not clear if degenerative changes can be ascribed to the effects of injection as opposed to the natural outcome of tendinopathy.

In an editorial reply to Ford and DeBender, Neustadt emphasized the increased risk of injecting the Achilles tendon in a patient with inflammatory arthropathy because to do so makes tendon degeneration more likely [115]. Beskin and associates [110], in 42 patients with Achilles tendon ruptures, found the associated incidence of steroid injection to be 7.1%. The average age of their patients (mean 39.4 years) called attention to other variables, such as aging, in the occurrence of spontaneous rupture. Pain was prodromal in 21% of cases, implying that suppression of pain would be particularly unwise. Astrom and Westlin studied a group of patients who had partial rupture and a history of chronic Achilles tendon symptoms. In a logistic regression analysis only preoperative steroid injections in men were predictive of a partial rupture [117]. If surgical repair is required for spontaneous rupture, delayed recovery and healing are more prevalent in those patients with a history of previous

Achilles tendon injection (Leadbetter, personal observation). Similar clinical observations have been made by others.

Summary

Strong statements regarding the efficacy of anti-inflammatory medication are based primarily on experience with rheumatic disease. Such experience, over 32 years, involving more than 400 000 injections in more than 12 000 patients, has led Hollander and associates [118] to conclude that *"No other form of treatment for arthritis has given such consistent local symptomatic relief in so many for so long with so few harmful effects."* Such endorsement has not been clearly transferable to tendon injury. Anti-inflammatory medications can unquestionably affect excessive inflammation. Whether this tissue effect is significant with regard to enhancing performance has been difficult to prove. To quote former Baltimore Orioles baseball pitcher Jim Palmer [119]: "Cortisone is a miracle drug . . . for a week!" This is because, in rheumatologic disease, inflammation is the problem, whereas intratendinous injury represents a degenerative process; as such, recovery depends on restoration of both the injured tissue and its kinetic environment [17]. The tendency to place an inflammatory label (i.e. "itis") on tendon pain has promoted the value of anti-inflammatory treatment while risking a de-emphasis of the role of physical rehabilitation and even well-timed surgical repair. If pain and signs of inflammation are persistent, repeated efforts to turn off the body's alarm are not a substitute for finding the cause of the fire. Indeed, to disable the "fire alarm" of pain from the site of an injury can clearly place the patient in greater jeopardy with respect to tissue overload and failure. Perhaps the greatest criticism that can be raised regarding anti-inflammatory treatment as a sole solution in tendon injury is that it tends, in its worst application, to be too passive and dependent a modality and does not challenge the patient's sense of responsibility to properly recondition, and to avoid abuse. Thus anti-inflammatory therapy may succeed only if the patient has been instilled with the proper expectations and responsibilities.

Increasing knowledge of the pathobiology of chronic tendinopathy and the various treatments required for complete recovery has led the experienced clinician to rely far less upon anti-inflammatory medication as a long-term solution. Until more biologically active drugs become available, the judicious application of anti-inflammatory therapy remains a sometimes useful but unpredictable adjunctive therapy for both acute and chronic tendinopathy. The successful clinical rationale is best arrived at not by random selection but by cautious individualized prescription.

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23
The Effect of Therapeutic Modalities on Tendinopathy

Jason D. Leadbetter

Degenerative tendon problems often prove recalcitrant to many forms of non-operative care [1]. Frequently, optimal functional outcomes and patient goals are not attained due to the persistence of chronic pain, loss of motion, and weakness. Ideally, rehabilitative goals should rely upon evidence-based clinical practice applied at appropriate intervals to facilitate healing and repair of injured tendons. In practice, understanding when and how to use therapeutic modalities to aid in healing and the recovery of function can often be unclear. For the therapist, modalities serve as an adjunct to directed exercise and have historically been utilized in the treatment of soft tissue injuries to decrease pain, inflammation, and edema, or to increase tissue extensibility [2]. In the era of evidence-based practice, the challenge is to relate the use of therapeutic modalities to demonstrate a healing response or the advancement of a specific functional goal. Recent histopathological studies of degenerated tendons have demonstrated varying underlying pathologies; the role of inflammation in intratenonous injury may be overstated [3]. The diagnosis of "tendonitis" often overshadows the histopathological evidence of degenerative tendinosis [3–5]. However, paratenonitis clearly has an inflammatory pathobiology. Therefore, the clinician must have an understanding of the mechanism of tendon injury and underlying pathology in order to deliver the most appropriate care. At question is whether the current accepted practice of employing modalities in tendon injury treatment is valid given the cellular pathology associated with tendinopathy and can their use be matched with a quantitative functional outcome measure. This chapter will examine the best available evidence on biological and functional efficacy of therapeutic modalities.

Classification of Modalities

Therapeutic modalities generally fall under four main categories: heat, cold, electricity, and manual therapy. Alternative modalities such as cold lasers, low energy extracorporeal shock wave treatments, and acupuncture are used widely throughout Europe and Asia and are gaining wider acceptance in clinical practice in the United States. In a general sense, clinicians utilize each classification because they generate a specific physiological effect upon an injury site that in theory can aid the recovery process. For example, heating modalities are most often used to increase tissue extensibility prior to stretch, decrease pain or to increase blood flow to an injured area. In a healing tendon, induced hyperemia may allow for increased removal of waste products, synthesis of new collagen, and increased production of fibroblasts [6,7]. By impacting functional impairments such as stiffness and pain, the appropriate use of heat by therapists and trainers can speed up the recovery phase of treatment and prevent the onset of new injury or chronic dysfunction. In theory, the correct use of an applied heating modality can directly impact both the rate and quality of return to function without limitation. This methodology of care holds true for the use of any physical agent, but difficulty arises for many clinicians trying to understand the mechanism by which their use is able to impact tissue pathology and affect outcome. Understanding the basic science helps explain the physiological affects of each therapeutic modality and serves as a foundation for clinical practice.

Basic Science

It is currently unknown whether the use of physical agents upon tendinopathy should be distinguished from other soft tissue injuries. The following is a discussion of the known biophysical effects of the main therapeutic agents.

Heat: Therapeutic heating modalities are generally separated into 2 categories: superficial and deep. Superficial agents involve the external application of heat by means of hot packs, infrared lamps, whirlpools, paraffin baths, and fluidotherapy. Deep heating modalities include

Table 23-1. Physiologic effects of heat application.

	Short heat application (30 min or less)	Prolonged heat application
Skin capillaries	Dilatation	Continued dilation
Skin texture	Smooth	Smooth
Skin color	Pink, then red	Dusky
Skeletal muscle	Relaxed	Irritated
Cell tissue size	Expanded	Less expanded but still above normal
Tissue pressure	Increased	Levels off
Tissue metabolism	Increased	Levels off
Pulse	Slow	May increase
Respiration	Slow and deep	May increase
Heart stroke volume	Decreased	Increased
Blood pressure	Increased then decreased	Decreased
Pain sensation	Decreased	Effect depends on extent of heating

Source: Reprinted from Rivenburgh DW (1992). Physical modalities in the treatment of tendon injuries. Clin Sports Med 11:645–659

ultrasound and diathermy. Table 23-1 illustrates the physiologic effects of heat application, which are generally considered to be the following: increases in tissue temperature, cellular metabolism, nerve conduction velocity, vasodilation, and decreases in pain, joint stiffness, and muscle tone and spasticity [2,6,8]. Clinical research supports changes in tissue extensibility with applied heat, and the effect of temperature on cellular activity is well documented [6,9,10]. Increases in thermal bond strength after tendon repairs with controlled heating and cooling has been demonstrated, while other research indicates degradation of different collagen types in tendon with elevated temperatures above 41 degrees C [11,12]. The lack of controlled studies of thermal modalities suggests the effect of heat upon tendinopathy is not well understood.

Superficial heating modalities accomplish the transfer of heat energy primarily through processes of conduction, convection and radiation. Most studies of the application of superficial heating modalities indicate that increases to local tissue temperature occur only to a depth of a few millimeters, do not exceed a peak of 104 degrees Fahrenheit, and can only be sustained for short periods [2]. According to the first law of thermodynamics, energy can neither be created nor destroyed but transformed into different states. The movement of atoms and molecules within an object is called kinetic energy and is a representation of an objects internal thermal energy. Thermal conductivity involves the transfer of this energy from an object of higher energy to an object of lower energy when two objects are in direct contact [10]. The use of hot packs and paraffin baths follows this principle. In general, the flow of energy from heating modalities goes from the higher energy modality source to the tissues of the body, which contain lower internal kinetic energy. In physical agents involving therapeutic cold, this flow is reversed with higher energy in the form of heat being drawn away from the body causing soft tissue cooling. Substances in the human body vary in their ability to act as efficient conductors of thermal energy based upon differing specific heat capacities. Bone, blood, and muscle are relatively good conductors compared to fat, which does not contain as much water fluid content and is considered a more efficient insulator [2,10].

Instruments such as infrared lamps utilize a slightly different process of heat energy transfer known as radiation. All objects can emit or receive radiant energy based upon the characteristics of the electromagnetic waves being produced by a certain object. The base unit of radiation is the photon, a measure of high-velocity molecular movement and the release of kinetic energy from molecular collisions. Photons travel along electromagnetic waves and energy is transmitted along varying frequencies. Higher frequencies are associated with shorter wavelengths along the electromagnetic spectrum, creating an inverse relationship between intensity of energy transmission and size of wavelengths. The energy contained in an infrared wavelength causes an increase in the molecular kinetic energy of the absorptive surface thereby increasing its thermal energy [8].

Fluidotherapy and whirlpools utilize a combination of convection and conduction as the mode of thermal energy transfer. Convection involves the movement of heated molecules from areas of high density to areas of low density. Thermally charged molecules display greater movement secondary to increased kinetic energy and thus require more space. Lower density heated regions are lighter and rise to replace higher density cooler regions moving in the opposite direction. This process creates circulating temperature gradients that continue

until all the thermal energy is equally distributed throughout the entire substance. Heat is then conducted to or drawn away from soft tissue immersed in a bath of water or sand kept at a unified temperature through mode of convection [2,8].

There are 2 types of deep heating modalities used clinically: diathermy and ultrasound. Ultrasound and diathermy are unique in that both have thermal and nonthermal properties. By using a pulsed rather than continuous setting, a clinician can stimulate mechanical cellular events that are critical in the stages of inflammation and repair. Although the literature is inconclusive, some effects that are thought to occur include: increases in fibroblast and macrophage activity, increases in microperfusion and cell permeability related to acoustic streaming and cavitation, increases in mast cell degranulation and release of chemotactic factor and histamine [2,6,13–15].

Thermal properties of ultrasound and diathermy are generally elicited when using a continuous mode. Both ultrasound and diathermy have been popular choices for many clinicians over the past several decades due their capacity to safely heat deeper structures. Deep heating modalities are generally considered indicated when one is trying to increase the temperature of tissues 2 to 5 cm beneath the surface of the skin [2]. The basic physiological responses to this mode of heating are the same as for superficial heating agents but are more penetrating. Although both ultrasound and diathermy accomplish the transfer of heat energy, the mode of transfer is completely different. Diathermy utilizes the properties of electromagnetic waves generated by highly conductive metal coils whereas ultrasound relies on acoustical energy.

There are 3 main types of diathermy: longwave, shortwave, and microwave. Theoretically, diathermy is able to effect heating of deeper connective tissues due to utilization of longer wavelengths and lower frequencies along the electromagnetic spectrum. The kinetic energy carried along these wavelengths is not refracted or absorbed as much at the surface level as is infrared energy, but is instead transmitted to a deeper level where the conversion to thermal energy occurs [16]. Of the different types of diathermy, short wave is most commonly used, followed by microwave. The use of longwave diathermy is no longer in accepted clinical practice due to the potential for serious burns and mechanical disruptions caused by frequency type.

Shortwave diathermy has two modes of application referred to as condenser field and induction field. Condenser field diathermy involves positioning a part into a magnetic field generated by separate capacitor plates where induction field diathermy utilizes physical contact of the capacitor plates on the patient to complete a circuit and generate the electrical field in line with the body. Although there are slight variances in the heating effect between the two types of electrodes, general thermal effects on soft tissue have been demonstrated to occur at depths of between 2 and 3 cm.

Microwave diathermy has a different application utilizing a shorter wavelength and higher frequency (2450 mHz) and follows laws governing the absorption of radiated energy. Studies have shown that microwave diathermy is less effective than shortwave because of reflected energy into fatty tissue [16]. Regardless of the type of diathermy being used, it is hard to locate correlative information in the literature describing impact on tendon healing properties.

Ultrasound differs from diathermy in that it uses acoustical energy to generate heat. An ultrasound machine utilizes common house current and converts it to an ultrasonic wavelength by means of the reverse piezoelectric effect. As AC current is passed through a crystal, the crystal becomes deformed in the direction of the current. A process of compression and elongation causes mechanical vibrations of the crystal resulting in oscillatory pressure waves in the frequency of the electric current being applied to the crystal [2]. Ultrasound waves are transmitted from a transducer or sound head to the patient through means of a homogenous coupling medium typically either a gel or water. Ultrasound energy can be attenuated, refracted, or reflected, depending upon the type of biologic tissue being impacted and the wave frequency. Clinically, a 1-MHz continuous mode setting is used to accomplish thermal effects at a depth of 2 to 5 cm whereas a 3-MHz frequency is used superficially for depths less than 2.5 cm [2]. Measurable tissue temperature increases have been documented using continuous mode ultrasound [2,9]. Pulsed low-intensity settings are reserved to generate the nonthermal effects described earlier.

Another unique application of ultrasound is phonophoresis. Phonophoresis utilizes the low-level force generated by ultrasonic waves to assist the transdermal delivery of medication. Different types of medications can be applied locally to effect inflammation, pain, and wound healing, but there is little evidence in the literature to support any significant effect [17].

Cold: The effects of therapeutic cold modalities are predicated on the same thermodynamic laws as heat. The application of a colder object upon a warmer surface affects a transfer of thermal energy flowing in the opposite direction. The internal thermal energy of the warm contact surface (e.g. soft tissue) flows to the lower energy and temperature source in the form of a cold pack for example [10]. The rate of cooling upon soft tissue is dependent on several factors such as the thermal conductivity of a particular tissue type, area size, tissue thickness, and difference between cold modality and the outer skin. As with any treatment modality, care must be taken to avoid inducing tissue damage such as ischemic cell

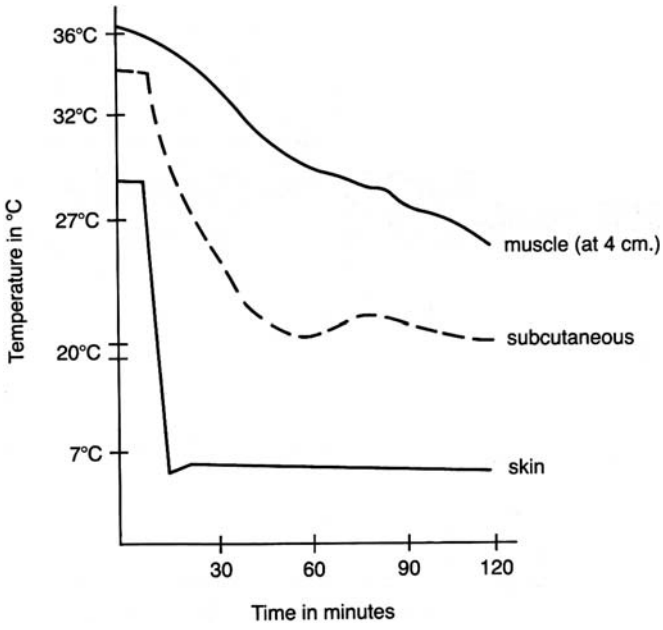

FIGURE 23-1. Tissue temperature changes during application of ice pack to the calf. (From Michlovitz, S [1986]: Thermal Agents in Rehabilitation. Philadelphia, F.A. Davis, p.75. as reprinted in Harrelson GL, Weber MD, Leaver-Dunn D. (1998) Use of Modalities in Rehabilitation. In: Andrews JR, Harrelson GL, Wilk KE, eds. *Physical Rehabilitation of the Injured Athlete.* 2nd edn. Philadelphia: W.B. Saunders; 82–145.)

death and nerve palsy [2]. The varying rates at which different biological tissues react when cold is applied are illustrated in Figure 23-1.

The physiological effects elicited by cold are generally considered to be the following: decreases in tissue temperature, pain, edema, nerve conduction velocity, muscle spasm, cellular metabolism, inflammation, tissue extensibility, and joint proprioception [2,6]. A review of the literature yields varying evidence as to the effectiveness of cryotherapy. Clinical research has supported the benefit of cryotherapy in controlling inflammation and cell metabolism after acute injury, but not as much is known about the use of ice to treat tendinopathy [4–6,18,19]. Numerous studies have demonstrated the impact of cold application at the cutaneous level but cannot support significant decreases in tissue temperature at greater than 2 cm below the surface of the skin. Deeper structures such as tendons may be affected by a hemodynamic interchange that occurs with the more superficial layers [19].

Some physiologic responses to cold, such as cold-mediated vasoconstriction and vasodilation responses, appear to be influenced by time of the exposure. Cold-induced vasodilation (CIDV) is a phenomenon that is purported to occur only after exposure times that are far longer than the 15 to 30 minutes that cold is commonly applied in the clinical setting [2]. There is also some evidence to suggest that the use of cold induces an increase in isometric muscle strength that is measurable for a few hours post-treatment. Concentric and eccentric muscle strength appear to decrease for a 10- to 20-minute period post-application after which no significant change from baseline strength occurs [20] (see Table 23-2).

Methods of therapeutic cold application include: conventional cold pack (chipped ice/bag), commercial cold pack (gel, chemical), ice baths (whirlpools, contrast baths), and ice massage.

Electricity: Therapeutic electricity is used to generate an action potential in excitable tissue. The type of physi-

TABLE 23-2. Physiologic Effects of Cold

	Short cold application (30 min or less)	Prolonged cold application
Skin capillaries	Constriction followed by dilation	Constriction (to prevent heat loss)
Skin color	White, then red	Rough, even more pronounced ("goose bumps")
Skin texture	Rough (due to action of the erector pilar), then smooth	
Cell tissue size	Little change	Slightly decreased
Tissue pressure	Decreased	Decreased
Tissue metabolism	Decreased	Decreased
Pulse	Quick, then rapid	Slow
Respiration	Gasp, then increased rate and depth of breathing	Decreased respiration rate
Heart stroke volume	Increased	Increased
Blood pressure	Increased	Decreased
Pain sensation	Decreased	Decreased

Source: Application as reprinted from Rivenburgh DW (1992). Physical modalities in the treatment of tendon injuries. Clin Sports Med 11:645–659

Table 23-3. Suggested uses of electrical stimulation

Re-education of muscle
Strengthening of muscle after injury
Control of pain in numerous acute and chronic syndromes
Control of postoperative pain
Control of labor pain
Treatment of urinary incontinence
Control of edema
Healing of wound
Healing of delayed or nonunion fractures
Functional electrical stimulation (orthotic)
Introduction of medications transcutaneously
Improvement or maintenance of range of motion
Stimulation of denervated muscle
Inhibition of spasticity
Relief of muscle spasms
Temporary increase of blood flow to an area
Treatment of neurovascular disorders involving vasospastic and pseudovasospastic disorders

Source: Reprinted from Harrelson GL, Weber MD, Leaver-Dunn D (1998). Use of modalities in rehabilitation. In: Andrews JR, Harrelson GL, Wilk KE (ed) Physical Rehabilitation of the Injured Athlete, 2nd edn. W.B. Saunders Co., Philadelphia, pp 82–145

ologic effect caused by an action potential can be varied by several parameters such as polarity, frequency, pulse duration, waveform, intensity, cycle type, electrode configuration, and treatment time [21]. The general indications of therapeutic electricity are given in Table 23-3.

The main units when considering applied therapeutic electricity are current, voltage, and resistance. The relationship between these variables is defined by Ohm's law: $I = V/R$. I = current, V = voltage, R = resistance. Voltage is the measure of the force which causes ions to move whereas current is the rate of electron movement in response to the applied force (voltage). Different types of materials (biological, chemical, physical) can either facilitate or inhibit the movement of ions. Resistors are materials with high impedance to ion flow. Examples of biological resistors include skin, fat, and bone. Materials in the body such as electrolyte solutions, water, and blood, act as good conductors and are characterized by low resistance [2,21].

Three types of current are used clinically: direct (DC), alternating (AC), and pulsed. Direct current involves the uninterrupted flow of charged ions in one direction. Direct current is typically utilized to stimulate denervated muscle or to drive different types medication transcutaneously during iontophoresis. Iontophoresis uses the repellant force generated by like charges to induce localized absorption of various medications into soft tissue. The efficacy of iontophoresis on tendinopathy is questionable [22].

Alternating current is defined by continuous ion flow in two directions, whereas pulsed currents involve either direct or alternating ion flow packaged into cyclically occurring waveforms. A clinician can choose between different waveform types such as monophasic, biphasic, polyphasic, symmetrical, asymmetrical, balanced or unbalanced, to produce different physical effects [21]. Examples of different waveforms are pictured in Figure 23-2.

Electromyographic units are used frequently in the clinic to measure the amount of electrical activity in skeletal muscle through either surface or implanted electrodes. Although EMG units do not involve applied electricity, biofeedback provides the patient and therapist useful information to facilitate neuromuscular control and relaxation of agonist or antagonist muscle groups during rehabilitation. This can be important when addressing the abnormal biomechanical stress that is either causing or impeding tendon healing.

Manual therapy: Manual techniques are generally used to increase range of motion (ROM), aid in the recovery of neuromuscular control and strength, decrease spasm and edema, and break adhesions that build around muscles, ligaments, capsular structures, and tendons [7]. Examples of manual therapy techniques include: friction massage, augmented soft tissue mobilization (ASTM), myofascial release, and active release technique. Tendon injuries involve changes in the cellular matrix [5]. This often results in a disruption of the normal longitudinal collagen fiber orientation of a tendon or ligament and a corresponding decrease in the ability to distribute mechanical load without strain. During the remodeling phase of healing, fibroblasts play a significant role in the synthesis of collagen, proteoglycans, and proteins important to the development of normal cellular matrix of a healthy tendon [5,7,25]. The proliferation of fibroblasts has been related to the type of load and stress placed upon a healing tissue [3,7]. Theories regarding the use of TFM (transverse friction massage) and ASTM (augmented soft tissue mobilization) suggest that new collagen synthesis results from the hyperemic response caused by the massage [23,24,26]. These forms of manually applied controlled trauma to a tendon performed at the right time in the healing process and with the correct intensity may actually induce the production of the fibroblasts and specialized proteins necessary for regeneration [23,24].

Other types of manual therapies involving active-assisted exercises and PNF techniques involve the application of an eccentric load. Some studies have indicated that a gradual and controlled eccentric loading component applied to a healing tendon also stimulates fibroblastic activity and aids in the recovery of parallel collagen fiber alignment [3,4].

Alternative modalities: There are numerous alternative therapeutic modalities currently undergoing closer

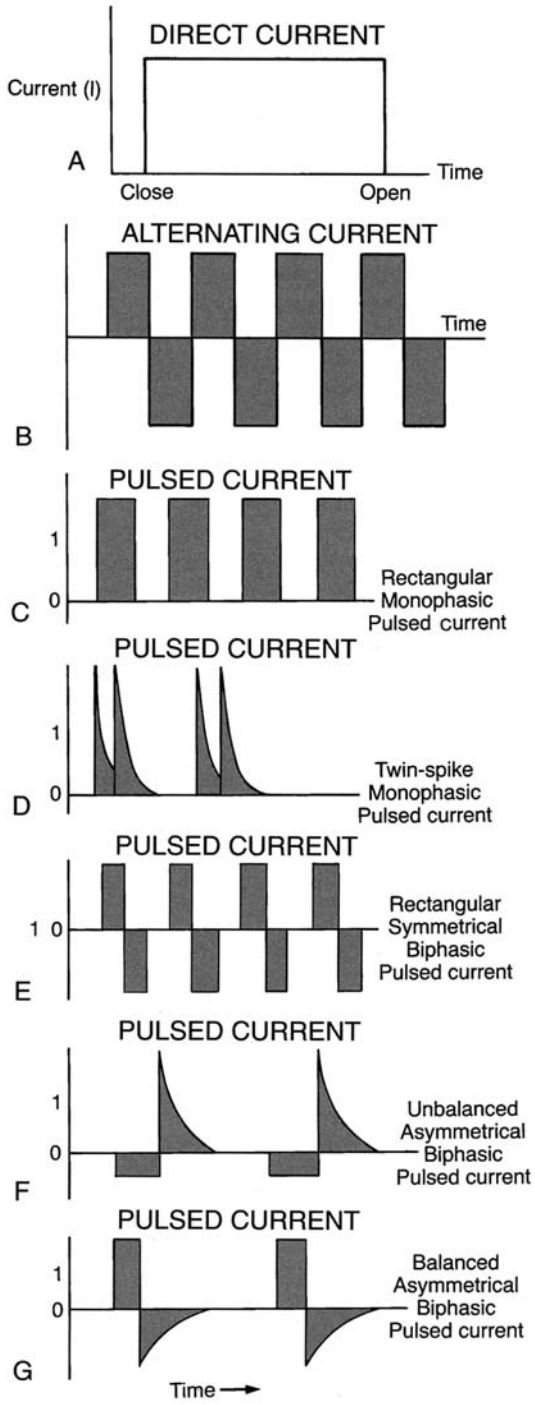

FIGURE 23-2. Graphic representation of the three types of electrical current. (A), Direct current. (B), Alternating current. (C) through (G), Pulsed currents. (Modified from Robinson A J. (1989) Basic concepts and terminology in electricity. In: Snyder-Mackler L, Robinson AJ, eds. *Clinical Electrophysiology.* Baltimore: Williams & Wilkins; 9,11,13. as reprinted in Harrelson GL, Weber MD, Leaver-Dunn D. (1998) *Use of Modalities in Rehabilitation.* In: Andrews JR, Harrelson GL, Wilk KE, eds. *Physical Rehabilitation of the Injured Athlete.* 2nd ed. Philadelphia: W.B. Saunders; 82–145.)

scientific review for effectiveness in treating soft tissue disorders. Extracorporeal shock wave therapy, cold lasers, and acupuncture are 3 treatments that are practiced more readily throughout Europe and Asia, but are gaining wider acceptance in the US through clinical trials approved by the FDA.

Extracorporeal shock waves can be generated utilizing electrohydraulic, electromagnetic, or piezoelectric devices. Treatments usually involve doses of either low-energy or high-energy waves that are then transmitted into biological soft tissue via an ultrasonic medium. Possible physiologic effects that are suggested to occur include the disintegration of calcifications, as well as cellular and circulatory changes associated with the regeneration of a healing tendon [25–31]. Efficacy studies on the use of extracorporeal shock wave therapy (ESWT) in the treatment of tendinopathy have shown mixed results. Loew et al. demonstrated improved patient responses to both pain and function after using shock wave therapy to treat insertional tendinopathies of the shoulder [27]. Another study evaluated the use of low-energy extracorporeal shock wave application to treat recalcitrant cases of plantar fasciopathy, with similar results [28]. Wang conducted a 2-year case series study on patients with lateral epicondylopathy of the elbow and showed positive results with respect to pain [32].

However, a double-blind, randomized controlled trial by Speed et al. on the effects of ESWT on lateral epicondylopathy purported to demonstrate a significant placebo effect with no positive effects compared to a sham therapy [33]. Buchbinder et al. showed similar results in their study on the use of shock waves for treatment of plantar fasciopathy [34]. Finally, findings by Haake et al. directly contradict reports of positive outcomes of ESWT as being flawed by inappropriate study designs [35]. At this time, further investigation needs to be conducted in order to substantiate positive clinical outcome.

Low-intensity "cold" lasers are purported to emit a form of electromagnetic energy that stimulates the production of fibroblasts, macrophages, and ATP. There does not seem to be a clear mechanism by which these effects occur although it is suggested that photochemical reactions drive the regulation and output of intercellular communication. A few studies have shown reductions in pain and dysfunction when using cold laser therapy to treat lateral epicondylopathy, trigger points, lumbalgia, and chronic pain. However, there is also conflicting evidence suggesting that there is no therapeutic benefit when compared to a sham treatment [36]. It appears difficult at this time to determine the true effectiveness of laser use until more empirical data is collected.

Acupuncture is an ancient Chinese healing art that proposes to utilize the body's nervous system to affect pain and dysfunction. Acupuncture points are stimulated

electrically through needles to induce biophysical signals that allow for healing responses to occur. Some controlled studies have indicated altered pain responses, but the mechanism by which acupuncture is believed to affect different types of healing and pain response in the body remains unclear [37].

Evidence-Based Medicine and Therapeutic Modality Use

As in other areas of medicine, the rehabilitation sciences are rapidly evolving through advanced clinical trials and the trend towards evidence based practice. The randomized controlled trial (RCT) is currently the gold standard for evaluating the significance of an intervention and its relative importance along a critical pathway. The best available evidence is typically analyzed using one of four types of guidelines: expert consensus, outcome based, meta-analysis and cost-effectiveness, and a combination of patient preference and evidence based [38]. Clinicians must demonstrate the effectiveness of their interventions using these guidelines and then correlate their findings with patient responses to pain and dysfunction. This approach has fostered controversy among many rehabilitation specialists as long held beliefs concerning the use of physical modalities in treating soft tissue injuries are coming into question.

In October 2001, an independent group of medical professionals, therapists, and researchers, collectively known as the Philadelphia Panel, released their findings based on a comprehensive review of the interventions used to treat various musculoskeletal conditions in the neck, shoulder, low back, and knee [39,40]. Randomized controlled, cohort, case control, and nonrandomized studies were collected and statistically analyzed utilizing the MEDLINE, EMBASE, Current Contents, Cochrane Controlled Trial Register, and CINAHL databases. The goal of this panel was to establish evidence-based treatment parameters regarding the use of exercise, traction, manual therapy, heat and ice, electrical modalities (E-stim, TENS, biofeedback), and ultrasound on soft tissue disorders ranging from arthritis to tendinopathy. Studies were allotted grades for clinical importance based on statistical significance and study design. For example, a RCT (single or meta-analysis) with a $P < 0.05$ was given a grade A, while a C grade was given to observational studies with low significance factors and low clinical importance (see Table 23-4). The results concerning the effect of physical agents upon the rehabilitation of tendon in the knee and shoulder were both revealing and inconclusive. Only 2 randomized controlled trials (one for ultrasound, one for therapeutic massage) were discovered for the treatment of tendinopathy of the knee. Of these 2, the study involving therapeutic massage was given a grade of C for affecting pain. For all other treatments, including ultrasound, the panel deemed there was either no data or insufficient data to attribute any clinical significance [39]. Concerning treatment of calcific tendinopathy, general tendinopathy, capsulitis, and bursitis of the shoulder, 4 randomized controlled trials and 3 controlled clinical trials were found. These studies involved the use of therapeutic ultrasound but only one study for treatment of calcific tendinitis received grade A for pain, function, and global patient assessment. All other treatments were classified as either having low clinical importance or having no or insufficient data to contribute to evidence based guidelines [40]. A full description of inclusion and exclusion criteria as well as general determinations of the Philadelphia Panel can be found in the journal *Physical Therapy.*

Robertson and Baker presented a meta-analysis of all studies concerning the effectiveness of therapeutic ultrasound on soft tissue healing [41]. A total of 35 RCTs were identified in a search of MEDLINE and CINAHL databases dating from 1975 to 1999. Exclusion criteria eliminated all but ten of these studies. Only 2 studies dealing with calcific tendinopathy and carpal tunnel syndrome

Table 23-4. Details of Philadelphia Panel Classification System

	Clinical importance	Statistical significance	Study design[a]
Grade A	>15%	$P < .05$	RCT (single or meta-analysis)
Grade B	>15%	$P < .05$	CCT or observational (single or meta-analysis), with a quality score of 3 or more the 5-point Jadad methodologic quality checklist
Grade C+	>15%	Not significant	RCT or CCT or observational (single or meta-analysis)
Grade C	<15%	Unimportant[b]	Any study design
Grade D	<0% (favors control)		Well-designed RCT with >100 patients

Source: Reprinted from Albright J, Allman R, Bonfiglio RP, Conill A, Dobkin B, Guccione AA (2001) Philadelphia Panel evidence-based clinical practice guidelines on selected rehabilitation interventions for shoulder pain. Phys Ther. 81:1719–1730

[a] RCT = randomized controlled trial, CCT = controlled clinical trial.

[b] For grade C, statistical significance is unimportant (i.e., clinical importance is not met; therefore, statistical significance is irrelevant).

could demonstrate an effect beyond that of a placebo [41]. Although definitive conclusions are not possible at this time, it does appear that a lack of evidence contributes to the confusion on the best way to treat tendinopathies.

An independent search of MEDLINE from 1970 to 2001 conducted by this author yielded similar results for effectiveness of physical agents upon tendon healing and regeneration. Keywords that were used either alone or in combination included: tendon, fibroblast, rehabilitation, repair, randomized controlled trial, and therapeutic modality. Although there are many descriptive studies concerning the use of heat, cold, electricity, etc., the literature is lacking in controlled studies correlating the specific use of a physical agent and the return of human tendon to normal function.

Recommendations for Future Use of Therapeutic Modalities

The dilemma facing rehabilitation specialists in today's evidenced-based climate is to relate clinical experience to clinical research. The specific use of a physical agent should correlate with the stimulation of tendon healing and have objective and quantifiable markers to guide the return to full function. The best and most timely care would be available to the patient if a clinician were to use cryotherapy, for example, and know that if it was applied at the right time, amount, duration, and intensity, measurable cellular events could occur in a tendon facilitating repair and return to premorbid function. However, efforts to improve clinical practice may also serve to inhibit this process if varying human inferences are made upon information gathered in databases that is either incomplete or irrelevant [42]. Functional outcome measures and quality-of-life indexes must continue to be emphasized as much as focusing on the singular tissue effect of any one treatment. Meanwhile, on going scientific investigation will be integral in guiding the use of therapeutic modalities.

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24
Rehabilitation After Tendon Injuries

Sandra L. Curwin

Introduction

Rehabilitation after chronic tendon injuries is a challenge. A variety of treatment options is available, but there is little evidence to support one approach or another. Views differ about the nature of the injury, diagnostic criteria and prognosis, natural history, evaluation methods and assessment of outcome. Recent Cochrane systematic reviews of Achilles tendinopathy concluded: "There is not enough evidence about the best way to relieve a painful Achilles tendon [1,2]." The recovery pattern after tendon ruptures, or accidents like the severing of hand flexor tendons, is fairly well-defined and follows the identified stages of healing, but the (usually) insidious onset and slow recovery in chronic tendon injuries make it difficult to plan treatment scientifically. The nature and extent of the injury, the stage of healing, and the tissue's mechanical state are largely unknown, since the onset time is not known. The physiological state of the tissue can only be estimated, and designing a treatment strategy based on the stage of tissue healing is difficult. This may result in prolonged disability, and a dilemma for both patients and care providers.

This chapter describes the use of exercise for rehabilitation of patients with chronic tendon injuries, and highlights the theory and science behind recommended interventions. The focus is on tendon injuries for which no direct traumatic cause is evident. The rationale for the treatment of these injuries often emerged from the treatment of other tendon (or ligament) injuries, so other interventions will be described when appropriate, but the focus of this chapter will be on the use of exercise as a modality in treating tendon disorders.

Normal Tendon Physiology and Mechanics

Tendons transmit the forces generated by muscles to bony attachments. They are not just passive structures, but also store and release mechanical energy, acting as springs during activities [3,4]. The tensile strength of a tendon is about 4 times the maximum force produced by its attached muscle. Tendons *in vivo* are rarely stressed to more than one-quarter their maximum physiologic strength [5]. Transducers implanted on animal tendons showed strains within the toe region of the stress-strain curve (3% to 4 % strain; Figure 24-1) during normal daily activities such as walking and trotting [6]. Therefore, there is a large margin between physiologic and maximum loading, at least during everyday activities of animals. Animal tendon loads, however, may not be representative of the loads to which humans subject their tendons during athletic activities. Indeed, even animal tendon loads can vary widely. A startled kangaroo rat generates Achilles tendon forces much larger than the values observed during most physiological activities (175% of maximum voluntary contraction vs 40% to 60%) [7].

Stress-Strain Curve

Data on human tendon loading are usually estimated through indirect calculations based on biomechanical models, and direct and indirect calculations do generate similar results [7]. The ground reaction force is used in conjunction with a visual image of the limb to calculate

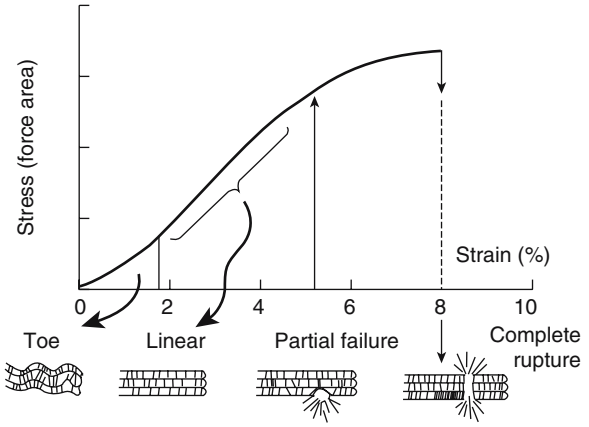

FIGURE 24-1. Stress-strain curve for tendon. The stress (F/A) and strain (% change in length), when plotted against one another, show the toe and linear and linear regions where most physiological loading takes place. The "overuse" theory of tendinopathy holds that some fibers rupture as the tendon is elongated into the upper linear region. Complete rupture occurs at 8% to 10% strain. (Reprinted with permission from Curwin SL. (1998) The aetiology and treatment of tendonitis. Ch. 4.4.4. In: Harries M, Williams C, Stanish WD, Micheli LJ, eds. *Oxford Textbook of Sports Medicine*. 2nd ed. Oxford, England: Oxford University Press, Figure 4, pg. 612. Ref. 82.)

a joint moment, which is then divided by the tendon moment arm to calculate the tendon force (see Figure 24-2). Barfred thus estimated a maximum Achilles tendon force of about 4340 N in a person who, while running, suddenly changed direction and ruptured his Achilles tendon [8]. I used the same method to estimate Achilles tendon forces of approximately 2500 N for a similar push-off activity involving a sudden change from backward to forward motion [9].

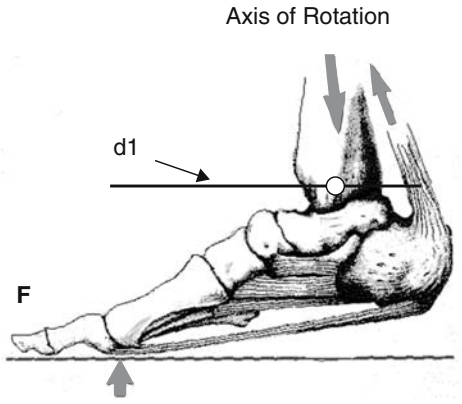

FIGURE 24-2. Indirect calculation of tendon forces. The ankle moment (Fx d1) is divided by the moment arm of the Achilles tendon (d2) to calculate the Achilles tendon force. This is typically calculated for each frame of the film capture of a movement, using force platform data for the ground reaction force and its location (F).

Data obtained from *in vitro* testing of human tendons have shown maximum tensile strengths of about 4000 N. Hence, human tendons *may* be loaded maximally during activities [8–14]. Achilles tendon forces from 2000 to 5000 N have been estimated in activities such as running and jumping, and tendons may often be loaded to more than 4000 N during athletic activities (see Table 24-1). Gregor and Komi placed buckle transducers on the Achilles tendons of human volunteers (including themselves!) and recorded forces in the range of 5000 to 6000 N during cycling and running [13]. Fukashiro et al. [14] used similar technology to measure forces in the Achilles tendon and found larger forces during hopping (3786 N) compared with jumping (2233 N). Some of the confusion about whether tendons are exposed to potentially damaging forces during activity may arise from the definition of what is considered "physiologic loading." Forces during walking and light exercise, physiological activities for many people, may only be 20% to 30% of those observed during vigorous exercises, yet the latter are physiological for most athletes. Therefore, tendons are actually injured far *less* often than could be expected given their frequent exposure to potentially damaging loads.

The most common theory concerning the etiology of chronic tendon injuries is that they are due to "overuse" from repeated loading into the higher linear region of the stress-strain curve, causing microfailure of the tendon's fibrillar structure. Though physically intact, microscopic ruptures, or even diminished lateral cohesion between collagen fibrils, may reduce tensile strength of a tendon. Such damage occurs not only as a result of tissue loading but also during rapid *unloading*, perhaps as a result of shearing within the tendon [15]. The rate of tendon deformation, as well as the magnitude of loading and the amount of deformation, may well be important factors in chronic tendon injuries.

TABLE 24-1. Estimated tendon forces during activities

Activity	Tendon	Force (N)	Reference
Running (slow)	Achilles	4000–5000	8,12
	Patellar	7000	9
Running (fast)	Achilles	8000–9000	8
Walking	Achilles	1000–3000	12
Cycling	Achilles	5000–6000	12
Push-off	Achilles	2000–4500	7,8
Jumping (take-off)	Patellar	7000–8000	10
Jumping (landing)	Patellar	5000–7000	9
	Achilles	2200–3500	9,10,13
Hopping	Achilles	3800	13
Weightlifting (rupture)	Patellar	14000	94

The breaking, or tensile, strength of a tendon is the magnitude of the force applied when the tendon ruptures [3,12,16]. Tensile strength may not necessarily tell us much about clinical cases of tendinopathy, since tendons rarely rupture under normal loading conditions unless previously injured or already diseased [16]. The tendon probably functions in the toe and low linear regions under most physiological loading conditions, and recent *in vivo* human tests suggest that strains of 6% or more may occur [17,18]. The slope of the linear region of the curve ($\Delta F/\Delta L$), the *stiffness*, may thus be a better indicator of a tendon's *in vivo* mechanical behavior [19,20]. Understanding the physical changes occurring in the different portions of the linear region of the stress-strain curve may be more important in explaining the tissue damage that occurs during tendinopathy than is a knowledge of the maximum load the tendon can tolerate before breaking.

The functional mechanical behavior of a tendon, in the normal anatomical setting, can be influenced by several factors:

- Size—a larger tendon can withstand more force.
- Length—a longer tendon can elongate further under the same load.
- Amount and type of collagen concentration—a higher concentration of collagen, or a higher proportion of Type I collagen, or larger collagen fibrils, will all create a stronger tendon.
- Amount and type of crosslinks—increased crosslinking indicates a stiffer tendon that will deform less under the same loading conditions.

All these factors can affect the force-elongation curve, but only changes in tendon composition will alter the stress-strain curve, since it is independent of both size and length. Size-dependent features are the *structural properties* of a tendon, while features related to tendon composition are the *material properties* of a tendon [21]. Changes in either structural or material properties (or both) can affect a tendon's functional mechanical ability, but reflect different adaptations. An increase in tendon size or length can mean simply the production of more tendon by the existing cellular components (like muscle hypertrophy), while a change in collagen concentration or type, or different crosslinking patterns, suggests a more fundamental change in the cell's synthetic pattern or a change in extracellular processing events such as crosslinking. Tendons can adapt in both ways to alterations in their physiologic milieu.

Effects of Exercise on Connective Tissues

Exercise has systemic effects on many body systems, including connective tissues, as well as local mechanical and physiological effects on structures directly involved in a specific exercise. Exercise influences cell shape and physiological functions locally, and also can have a direct mechanical effect on matrix alignment [22,23]. The response to exercise varies among tissues, and depends on the nature of the stimulus, as well as the amount, type, and frequency of loading [24,25]. Muscle responds to increased mechanical load by increasing myofiber cross-sectional area, primarily by synthesizing more force-producing protein. An increase in frequency of loading (with no change in magnitude) will result in alterations in metabolic enzyme profiles [26]. Eccentric exercise may produce muscle damage [27,28], while sustained increased loading increases the connective tissue component of the muscle [29]. The molecular program of muscle adaptation to endurance exercise and resistance exercise is very different [30], but in each case the adaptation improves the muscle's ability to function under its new loading conditions. The tissue adapts in different ways to different stimuli.

The local mechanism of connective tissue (bone, tendon, ligament, and cartilage) response to exercise may involve cells detecting tissue strain and modifying the type and amount of tissue synthesized [22–25]. Increases in collagen turnover and prostaglandin production have been measured in the peritendinous space around the Achilles tendon after endurance running [31,32]. The expression of numerous genes increases during periods of rapid tendon growth [33]. The volume, nature, and frequency of deformation are important. Compressive loading will induce bone or cartilage formation [34–39], while tensile loads will result in tissue resembling that found in tendon or ligament [37–40]. Tendons also can vary in composition along their length, or width, according to the distribution of load, and the presence of compressive forces as the tendon wraps around bony structures [38,39]. Mechanical loading does modify tendon composition.

Maintenance of the normal mechanical state of connective tissues appears to require repetitive loading beyond a threshold level [40]. Loading below this level results in weaker tissues, and these changes take place quite rapidly. The effects of disuse and immobilization on tissues such as muscle, ligament, joint capsule, and tendon have been well established [41–49]. All musculoskeletal tissues atrophy under decreased load. In tendons, both collagen and crosslink concentration decline, and the tissues becomes weaker through both structural and material changes [45]. These findings have led to the clinical use of early motion and gradual stress application to treat bone and soft tissue injuries [51,52].

Connective tissues also adapt to increased loading by becoming stronger, but these changes occur over a longer time frame than with disuse [20]. Healing and normal tendons both adapt to increased loads either structurally, by becoming larger and hypertrophying as muscle does, or by changing their material properties to become stronger per unit area [51–53]. Almost all musculoskele-

tal tissues respond to increased load with increased tensile strength [46]. Muscle rapidly hypertrophies under increased load, and may also increase its connective tissue content [29]. Other connective tissues behave in a similar fashion [52–63].

Various tissues respond differently to exercise, but there also are variations in the response of a given tissue to different types of exercise. Different regions of ligaments respond differently to immobilization and recovery (Figure 24-3) [20], with junctional areas of ligaments responding more rapidly to immobilization than the midsubstance, but recovering more slowly. If tendons behave the same way, it may help explain why some tendon injuries often occur at bone-tendon junctions. Chronic mechanical overload (via surgical muscle excision and compensatory hypertrophy) on a tendon results in both structural changes (increased cross-sectional area) and material changes (alterations in crosslinking patterns and amounts) [59] (see Figure 24-4). Running is often used experimentally as a model of tendon loading, but the results after such endurance exercise are variable in comparison to chronic overload, perhaps because the load is applied for shorter periods. Running has little effect on tendon size and composition in some studies [53,58], while others have found changes in tensile strength or stiffness [60–63]. Swimming showed little or no effect on healing rat tendon [63], but increased tendon strength in another study [65]. Since loading magnitude is much lower in swimming compared with locomotion [66], it is difficult to see why tendons would become stronger as a consequence of such activity. The number of cycles may be more important than the load per cycle in tendon adaptation to exercise [65]. Endurance exercise seems to produce more variable results, perhaps due to variations in loading magnitude, number of cycles, accompanying physiological stress, etc.

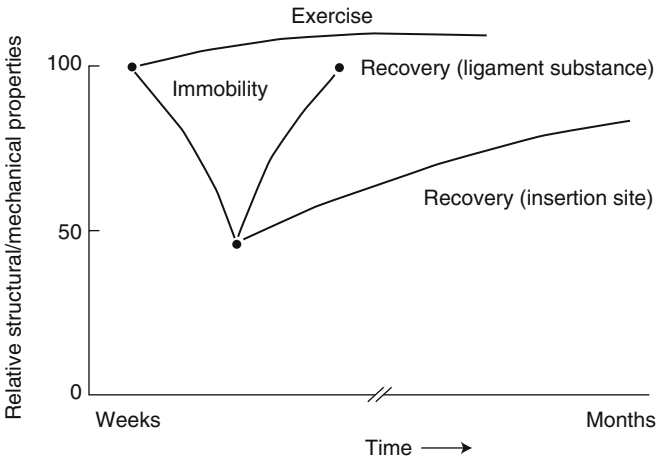

FIGURE 24-3. Regional responses to loading. Different regions of ligaments and tendons respond more or less rapidly to immobilization. The effects of immobilization occur fairly rapidly, while recovery, or strengthening above normal, takes much longer. (Redrawn with permission from Woo SL-Y, Gomez MA, Sites TJ, Newton PO, Orlando CA, Akeson WH. The biomechanical and morphological changes in the medial collateral ligament of the rabbit after immobilization and remobilization. *JBJS* 1987; 69A: Fig. 11, pg. 1210; Ref. 20.)

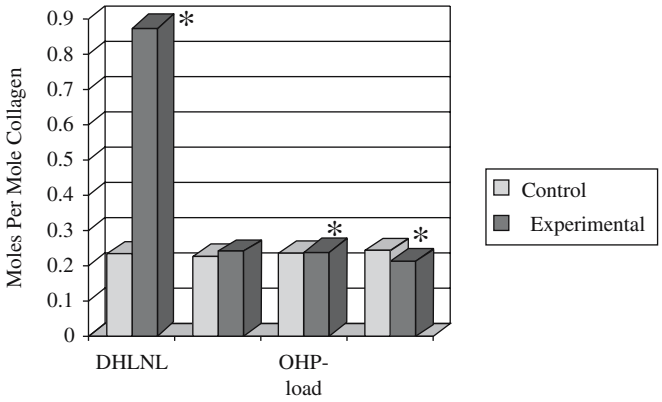

FIGURE 24-4. Crosslinking after changes in tendon loading. Chronic increased loading causes a change in the number of mature crosslinks (OHP), while running caused a decrease [53,58]. There also is a large increase in the number of precursor crosslinks to OHP (DHLNL), but not another immature crosslink (HLNL). This suggests that the pattern of crosslinking may be changed by mechanical load. [58]

Exercise and Injury

Running and jumping can stress tendons to large percentages of the theoretical maximum for mammalian tendon (Table 24-1). The association of tendinopathy or tendon rupture with particular sports, such as badminton's association with Achilles tendon rupture, implies that the high demands placed on tissues during movements in sports and dance may cause injury [67–71]. The occurrence of tendon injuries after sudden increases in the amount of training, or when training is resumed unchanged after a period of inactivity (and presumably after a tendon has weakened due to disuse), suggests that the tendon subjected to loads that now exceed its decreased tensile strength, thus damaging the tendon.

Some athletes, though, develop tendinopathy while training at the same intensity level (i.e. at the same loading magnitude). It is hard to imagine why previously well-tolerated loads should now produce an injury. The relationship between training intensity, load, and tendon physiology may be more complex than previously thought, and not all types of exercise have the same effect on tendon. The number and type of crosslinks in chicken Achilles tendon increased with chronically increased loads, but decreased with an intermittent strenuous running program, even though the latter increases the

load on the Achilles tendon and has often been used experimentally to increase tendon loading (Figure 24-4) [54,59]. Other physiologic effects take place during running, and some of these may offset the local mechanical effects of running exercise. Such effects might include stress responses, or immune responses, to strenuous physical activity. Interleukin-6 levels are elevated after exercise [72], and an endocrine response to exercise has been well-demonstrated [73–75]. These other, as yet unknown, factors may gradually induce changes in the tendon such that previously safe levels of loading are now capable of damaging the tendon.

The number of repetitions, and the recovery time after loading, also may play a role in tendon disorders. Each individual load may well be within the physiological range, but these loads are repeated so often that recovery cannot occur and, eventually, the structure fatigues [76]. Animal studies suggest that even low-force physiologic loads can cause tendinopathy if they are repeated often enough for long enough [76–78]. Cyclic loading induces peritendinous inflammation and inflammatory mediators by tendon cells, although no tendon degeneration was observed [77–79]. Stretching in the presence of inflammatory cytokines induces matrix metalloproteinase synthesis in rabbit tendon cells *in vivo*, while stretch alone had no effect [80]. Repeated exercise may induce tendon sheath inflammation, and exercise in the presence of tendon inflammation may amplify the production of collagen-degrading enzymes, perhaps causing, or increasing, tendon damage. One might conclude that adequate rest periods after repetitive loading would allow recovery to a normal physiological state, and targeted anti-inflammatory agents might have a protective effect against tendon injury.

Tendon Injury and Healing

The Injured Tendon

The most basic principle in the etiology of tendinopathy seems to be that the tendon is exposed to forces that cause damage to the tendon, although there is little direct evidence to support the view that mechanical forces cause tendinopathy [81]. Either the forces are too large for the tendon to safely withstand, the forces are applied too frequently for the tendon to recover, or the tendon structure or composition has changed so that "normal" forces are now causing injury. Viewing the situation simply, there are two possible solutions: to reduce the force applied to the tendon, or to change the tendon or its environment so that the same forces no longer harm the tendon. The nature of the actual damage may depend upon the *type* of force (compressive vs. tensile) as well as its *magnitude* and *pattern* of application, and each of these factors must be evaluated.

Type of Force

A tendon may be subjected to compressive, tensile, or shear force, but is best suited to withstand tensile forces. Abnormal *compressive* forces may cause an "extrinsic" tendinopathy [82]. The compression may come from a garment or a piece of equipment worn by the patient. For example, tight laces in a high-top sneaker or skate may cause paratendinopathy of the extensor tendons at the ankle joint, or the patient's own anatomical structures may be responsible [83]. A large acromion process may cause pressure on the supraspinatus tendon, leading to shoulder impingement syndrome, or a tight tensor fascia lata may contribute to iliotibial band friction syndrome [83,84]. Retinacula at the wrist can cause various forms of tenosynovitis, usually in combination with repeated use during occupational or recreational activities [83]. These examples of tendinopathy are best treated by early removal of the external cause, or by changing the anatomical environment through joint mobilization, flexibility exercises, or other appropriate exercise interventions. Compressive loading continued over a period will lead to changes in tendon composition as the connective tissue adapts to such mechanical stimuli by forming cartilage-like tissue [38,39]. These loading-induced changes in composition may exacerbate the clinical problem (say, by altering stress or strain distribution). On the other hand, they may be a successful adaptation that should be further encouraged.

Extrinsic tendinopathy also may be due to abnormal *tensile* forces that result from alignment or anatomical problems. Foot pronation, for example, might cause increased tensile stress on the medial side of the Achilles tendon [85]. Excessive pronation may be anatomical, or may result from excessive shoe wear. Thus, patients with chronic tendon injuries demand careful and thorough assessment of potential external causes (or contributors) before treating the tendon itself.

The Overuse Injury—Intrinsic Tendinopathy

Tendinopathy also may result from changes or inadequacies within the tendon, the so-called "intrinsic" forms of tendinopathy. The increased incidence of tendon injury after antibiotic administration or kidney dialysis suggests a close connection between alterations in tendon physiology and tendon dysfunction [86–89]. This connection is not clear in most clinical cases of tendinopathy, but, as there are no readily identifiable external causes, tendinopathy is attributed to a change, or degeneration, in tendon structure. It seems likely, however, that the loads applied to the tendon are inducing the change, except in cases involving genetic abnormalities or diseases affecting connective tissue structure [90,91]. The

tendon is simply not strong enough to tolerate the tensile loads to which it is subjected. There are two possible solutions: 1) remove or reduce the tensile forces; or 2) cause the tendon to become stronger. If the loading pattern is within normal limits for a given patient (or if the patient cannot reduce the load), force reduction probably is not a viable long-term solution. Many patients (professional athletes and dancers, workers with repetitive strain injuries) suffer from chronic tendon pain because they are unable or unwilling to reduce the forces applied to their injured tendons [92,93]. In such cases, an intervention, such as exercise, that will induce adaptation within the tendon may allow it to better withstand these loads.

This version of the etiology of "overuse tendinopathy" is probably the most familiar description of chronic tendon injury [81], and the exercise intervention strategies described in this chapter apply to this type of tendon dysfunction. Theoretically, the otherwise normal tendon has been chronically subjected to relatively large loads, perhaps extending into the linear region of the stress-strain curve [21], and this caused partial rupture (microscopic failure) of some of the fibrils within the tendon, or slippage between fibrils, leading to tendon injury [15,94]. Such injuries have been likened to the stress fractures that occur in bones subjected to chronic (over) load [76,94]. Since tendon structure recovers with rest, even after loading into the linear region, time (to recover) is probably an important element in producing these injuries, although we have little knowledge of the threshold of training frequency that may result in injury. Overuse tendinopathy develops gradually and may be related to high training levels. It may be appropriate to consider this another form of "overtraining," rather than mechanical overload, involving a combination of physiological and mechanical factors. This can be a helpful analogy when explaining this disorder to athletes, since most are familiar with situations where high intensities of training result in no improvement, or even a decline, in performance [76].

Not only high-level athletes are afflicted with this type of tendinopathy, although most of the eponyms that are used to describe chronic tendon injuries, such as tennis elbow and jumper's knee, are related to sports activities. Many individuals involved in recreational sports also suffer, as well as non-athletes involved in repetitive loading activities [92].

Sudden Loading/Excessive Force

Tendons may also be damaged by loading patterns other than chronic. Sudden force application, particularly involving lengthening (eccentric) muscle contractions, may lead to muscle or tendon injury [27,28]. Sudden maximum muscle activation results in a larger-than-normal force being very rapidly applied to the tendon, causing partial or complete rupture [7]. Large tendon forces are involved, usually in combination with maximum tendon elongation. The filming of a competitive weightlifter performing a lift during which his patellar tendon ruptured showed that the injury occurred as the lifter changed from downward to upward motion, i.e. at the end of the eccentric phase [95] (see Figure 24-5). The force on the patellar tendon was estimated at about 14.5 kN, over 17 times body weight. The combination of muscle-tendon length and maximum force production has also been associated with muscle-tendon injury. A gastrocnemius muscle strain was recorded on film during a cricket match: A defect in the muscle was observed just as the muscle-tendon complex moved from eccentric to isometric mode [96].

Sudden force application can cause more damage than force that is gradually increased to the same level of loading, and the sudden removal of a given force level is also more likely to cause disruption than a gradual reduction of the same force. The reasons for this are not entirely known, although it appears to involve disruption

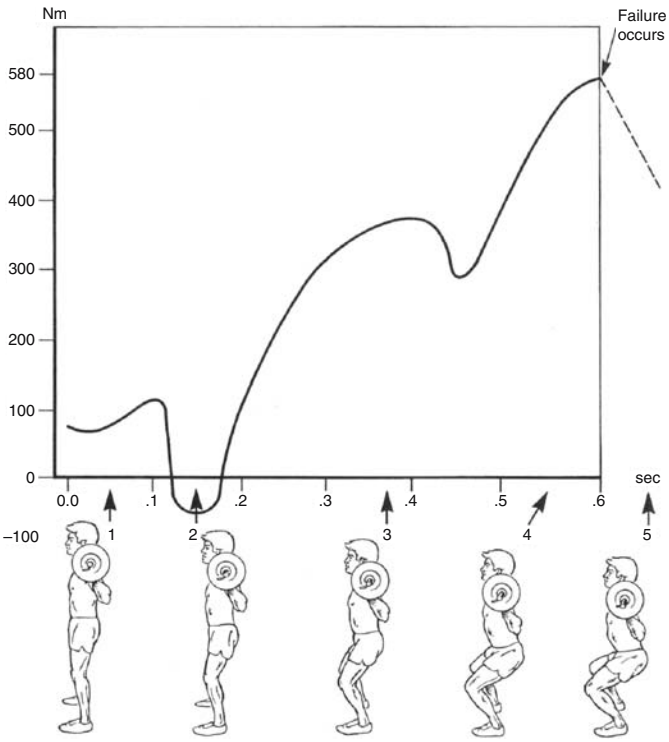

FIGURE 24-5. Patellar tendon rupture. A weightlifter was filmed during competition, and the moment of his patellar tendon rupture was captured on film. The rupture occurred at the transition from downward to upward movement, and a force of about 14 000 N was estimated to be acting on the tendon. (Redrawn with permission from Zernicke RF, Garhammer J, Jobe FW. Human patellar tendon rupture. *J Bone Joint Surg.* 1977; 59A; Fig. 3, pg. 181; Ref. 95.)

of the relationship between the collagen fibrils and their surrounding matrix [15]. A combination of maximum force production, sudden reversal of movement from eccentric to concentric loading, and rapid application and/or release of force seems to be particularly stressful to the tendon. This type of loading occurs in almost all athletic activities [97]. The terms eccentric and isometric refer to the overall behavior of the muscle-tendon unit, since it has been demonstrated that the tendon may be lengthening while the muscle is shortening. Thus, tendon deformation may occur even when overall muscle length remains constant [98–100].

Stress Distribution Within the Tendon

A tendon of uniform size and composition is generally assumed to have stress and strain distributed symmetrically across the tendon cross-sectional area and throughout its length. Changes in cross-sectional area along a tendon, however, will cause more stress at levels where cross-sectional area is smaller. Also, tendons are not uniform in composition throughout their length, implying that some regions may deform more than others in response to the same load [17,18,99,101,102]. This might help explain the relative frequency of chronic tendon injuries at the muscle- or bone-tendon junctions, as material properties change. Variations in strain in the medial and lateral Achilles tendon were observed under *in vivo* loading conditions when different sections of the gastrocnemius muscle were active, suggesting that tendon deformation can vary among different regions of the tendon [103]. This could lead to concentrations of stress or strain within the tendon, so that one part of the tendon is subjected to larger forces than others. If these areas are damaged and can no longer withstand loading, the remaining fibrils would be subject to higher loads, as in region 3 of the stress-strain curve. These remaining, as yet undamaged, fibrils would now be placed at higher risk under previously physiological loads.

Variations in loading within the tendon may also be related to motor control or muscle architecture. Tendon fascicles are associated with discrete motor units, and these fascicles are probably most heavily or directly loaded when their associated motor units are active [104]. Not every motor unit within a muscle fires during recruitment of the muscle. Rather, a cycling of motor unit firing takes place to maintain a given force level. Slow movement or maintenance of posture requires the use of small motor units composed of slow-twitch muscle fibers. The tendon fascicles associated with these motor units are probably regularly loaded during daily activities, and are probably "stronger," or more resistant to damage. Very rapid loading, or conditions requiring unaccustomed force production, can increase muscle force levels beyond those generated even during maximal isometric contractions, suggesting that some motor units are seldom recruited under normal loading conditions [7]. The tendon fascicles attached to the muscle fibers of these seldom-used motor units may have not been exposed to the same loading history as other fascicles within the tendon. Perhaps these tendon fascicles are weaker as a result of little or no loading during daily activities, and thus more easily injured when a sudden force is applied. This theory has been used to explain the muscle soreness and damage closely associated with eccentric muscle contraction, and it could apply to tendon as well [27,28,105]. Different types of muscle activation may therefore be useful in the recovery from, or prevention of, tendon injuries, and may help explain why resistance loading is beneficial in rehabilitation of chronic tendon injuries, even for patients who regularly load their tendons (such as runners). A repetitive loading pattern may use the same subset of motor units, while resistance training may recruit new motor units, thus loading different regions of the tendon. Whether the explanation is purely mechanical or also involves a neural element, it seems possible that there may be asymmetries in the pattern of loading and fascicle strength within the tendon, through variability in muscle fiber recruitment, muscle fiber lengths, fiber angles, force trajectories and force transmission [103,104].

Role of Eccentric Muscle Activation

Muscle fiber damage occurs after unaccustomed eccentric loading, and this damage is related to the type of contraction, not to the magnitude of loading, as similar damage does not occur after concentric exercise that generates the same force [27,28]. Force increases as the velocity of active muscle lengthening increases, while the opposite is true during concentric (shortening) muscle activations [106–108]. A tendon, being connected "in series" with a muscle, is thus exposed to larger loads during eccentric loading, especially if the movement occurs rapidly [109]. The tendon also is maximally strained during eccentric muscle activation, and this may help explain the frequent connection between eccentric loading and tendon injury [95,96]. This combination of maximum load and maximum deformation occurs in landing from or preparing for a jump (patellar tendinopathy) [11,99], midstance during running [9,85], during a demie plie in ballet [70], or on a push-off in badminton (producing Achilles tendinopathy) [71]. Shortening activations of muscle-tendon units usually are preceded by lengthening while the muscle is active. This activation pattern stretches the muscle-tendon unit (MTU), creating a passive force in the muscle due to the elongation of its elastic elements, and providing elastic energy *if* the muscle is allowed to shorten immediately after being lengthened [3,4,97–100]. This storage of elastic energy

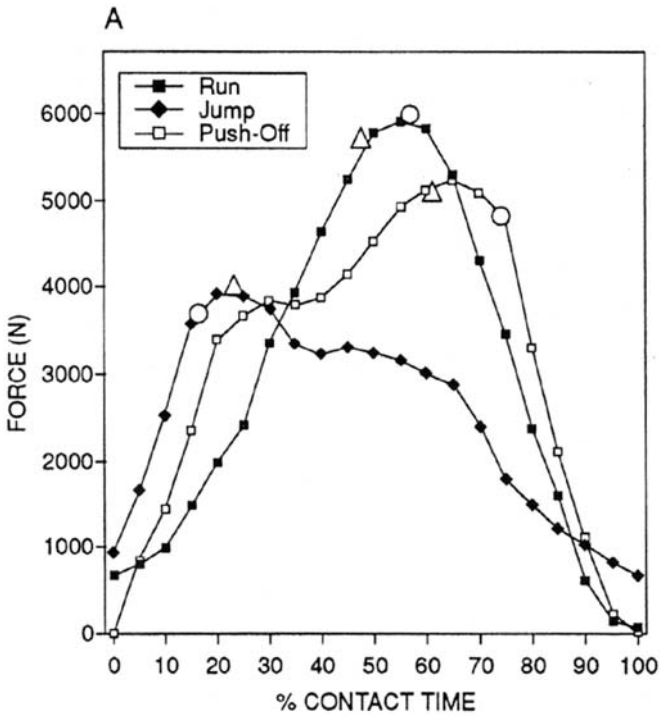

FIGURE 24-6. Achilles tendon forces during activities. Achilles tendon forces were estimated for three activities, using the calculation method shown in Figure 2; Run = running, Jump = landing from a jump; and Push-Off = a sudden change from backward to forward motion [8], see also Table 24.1.

allows the muscle to do more work at lower metabolic cost. It also results in maximum force and maximum elongation being simultaneously applied to the tendon, which may cause damage. Figure 24-6 shows the loading of the Achilles tendon during different activities and exercises [9]. When the kinematics and kinetics of these activities are examined, in nearly all cases maximum force production and maximum muscle-tendon length coincide. This occurs at the point where the muscle changes from eccentric (lengthening) to concentric (shortening) activation. Similar movement patterns coincided with injury in the two published cases where muscle-tendon injury was recorded visually [95,96]. The deformation of the tendon during such loading patterns has been reported to be in the range of 6% to 11% [17,18].

Other Factors Playing a Role in Tendinopathy

Endocrine

Some patients develop tendinopathy when no apparent change in loading or training has occurred, no external cause can be identified, and there are no examples of sudden, unexpected force application that the patient recalls. In such cases, the practitioner should be suspicious about systemic factors, especially if there are multiple sites of tendinopathy. If these systemic factors act gradually on the tendon, their effect would only be observed after a considerable time period. Endocrine responses to stress, such as increased glucocorticoid and catecholamine release, may have negative effects on connective tissue [110–113], increasing turnover and resulting in less mature collagen and thus decreased crosslinking [112,113].

Hormones can influence connective tissues such as tendon, and there are case reports of tendinopathy and tendon rupture in patients with kidney and thyroid disease [88,89,114]. Gender differences have been noted in tendon dysfunction, suggesting a hormonal influence [115,116]. This influence has been suggested for lateral epicondylitis (lack of estrogen) [117]. An endocrine response to chronic overtraining [118,119] may be at least partially responsible for some otherwise unexplained cases of tendinopathy, as there appear to be connections among hormonal response to training, carbohydrate metabolism, and systemic inflammatory mediators [119]. Whether the effects of systemic factors on tendon can be modified or offset by mechanical loading is unknown.

Other Metabolic Factors

Drug administration has been linked to tendon disease. Administration of fluoroquinolones, such as ciproflaxin, has been strongly associated with tendon disorders [86,87]. The relationship between chronic steroid administration and tendon rupture is well-known [113,120]. Presumably systemic changes cause an alteration in material properties as a consequence of tendon composition changes, such as decreased collagen synthesis [112]. The resulting weakened tendon then becomes vulnerable, even though loads remain unchanged.

Compressive Loading

The tensile strength of a tendon may gradually decline over time if it is subjected to chronic compressive loads, or if turnover is increased markedly, resulting in less mature crosslinking [38,39,44,47]. Less collagen, a change from Type I to Type II collagen, fewer collagen crosslinks, and more ground substance all result in decreased tissue tensile strength, and these changes all take place in tendons subjected to compressive, rather than tensile, loading [24,37–39]. Compressive loading may also result in regions of decreased blood flow in tendon, as has been demonstrated for supraspinatus tendinopathy [121]. Compression, and the changes it causes in tendon composition and mechanical behavior, is a large factor in rotator cuff tendinopathy, and this may suggest a role for

loading the supraspinatus tendon with tensile forces during rehabilitation to induce formation of "correct" new tendon tissue. Such tensile loading would be expected to induce a change in tendon composition if applied gradually, so that collagen content and crosslinking would actually increase.

Nutritional

The adequate amounts of amino acids supplied by a normal healthy diet are required for all protein synthesis, and this of course includes collagen. Cofactors such as vitamin A, vitamin C, magnesium and copper are important in collagen synthesis and crosslinking [90], and iron deficiency can have a negative influence on healing [122]. Collagen synthesis may be more severely affected than some other proteins during fasting [123], which may have implications for athletes involved in sports that emphasize a slender build, such as gymnastics and ballet. Nutritional factors in chronic tendon injury have not yet been explored.

Referred Pain

This is a frequently unrecognized cause of tendinopathy-like pain, and is due to peripherally located (somatic referred) pain resulting from irritation of spinal structures such as the zygapophyseal joint capsule, intervertebral disc, or a ligament [124]. It is frequently seen in patients with tennis elbow, where degenerative changes in the cervical spine cause symptoms which mimic exactly those of tennis elbow [125]. This may not be a common cause of tendon pain in the athletic population, but one should be suspicious if a "tendinopathy" fails to respond to treatment, and the physical therapist should *always* conduct a screening examination of the spine with peripheral examination, especially if the patient falls in the appropriate age category for degenerative spinal changes [126]. If decreased spinal range of motion or local joint signs are observed, these should be treated before management of the peripheral problem is undertaken.

Tendon Healing and Exercise

The healing process of severed tendons has been well described, using models where the tendon has been divided, surgically or accidentally, and the severed ends reopposed and held in place via immobilization or suture [127–133]. These models have contributed much to the understanding of tendon healing under these conditions. The initial inflammatory stage triggers an increase in glycosaminoglycan (GAG) synthesis within days. This is rapidly followed by collagen synthesis, such that the healing wound can be subjected to low levels of force within a few days [51,130]. The application of low levels of tensile force encourages the new collagen fibrils to align with the direction of force application, and healing tissues such as skin, muscle, ligament, or tendon subjected to progressive loading are almost always stronger than unloaded tissues [51,53,131–133]. The application of these principles in plastic surgery has led to the design of early motion programs after tendon repair, and a rehabilitation program based on scientific principles (see Table 24-2).

It is difficult to use these principles of healing to treat chronic tendon injuries. Tendinopathy can be classified as acute or chronic depending on the duration of symptoms (<6 weeks or >6 weeks), but this is arbitrary, and probably is not useful when dealing with injuries that have developed gradually and, in some cases, may have existed for years. The physiology of tendinopathy remains largely unknown. Little is known about the inflammatory response (if any) to the types of mechanical trauma that produce chronic tendinopathies. An injury which involves the tendon or its associated sheaths may be referred to as tendinopathy, but a plethora of other terms also exists: *tendinosis* (degeneration of the tendon without inflammation), *tenosynovitis* (inflammation of the sheath surrounding the tendon), *paratenonitis*, *peritendinitis* etc. Some authors argue that, with cases of chronic tendinopathy that developed very gradually and never appeared to have an acute stage, there is no associated inflammation of the tendon or the tendon sheath, only

Table 24-2. Clinical principles during healing after acute tendon injuries

	Stage of healing		
	Inflammatory	Proliferative	Remodeling
Time (days)	0–6	5–21	>21 days
Main aims	Avoid new tissue disruption	Prevent excessive muscle and joint atrophy	Optimize new tissue alignment and strength
Physiology	Promote synthesis of GAGs crosslinking Prevent prolonged Inflammation	Increase collagen amount Decrease crosslinking (joint capsule) Begin alignment of collagen molecules	Increase fibril size Increase (tendon) Increase alignment of collagen fibrils
Suggested therapy	Rest, ice Anti-inflammatory drugs or modalities	Very low tensile forces Modalities to increase collagen synthesis (ultra-sound, electrical stimulation)	Progressive tensile loading

degeneration within the tendon itself, and so the condition should be called *tendinosis* [134,135]. This conclusion initially was based primarily on observations of human tissue obtained during surgical procedures aimed at relieving chronic tendon problems. These observations may have represented the late, fibrotic stage of tendinopathy, and did not eliminate the possibility of the earlier presence of inflammation [136]. *In vivo* microdialysis measurement from the Achilles tendon showed no sign of typical inflammatory mediators, confirming earlier hypotheses [31,32,137]. Sudden tendon rupture without prior symptoms has also been attributed to tendinosis, since when these tendons are examined histologically, areas of degenerative change, which precede the actual tendon rupture, are evident. Yet, pain persists in most cases of tendinopathy, and swelling is often present as well: both are cardinal signs of inflammation [138]. It has been suggested that other substances, such as glutamate [139], or reactive oxygen species [140], rather than typical inflammatory substances, may be responsible for tendon pain.

A major difficulty in scientifically evaluating chronic tendinopathy has been the lack of a suitable animal model for chronic tendinopathy. Most animal models used partial laceration or chemical injection to induce a tendon injury, which may not closely represent naturally-occurring injuries. Racehorses frequently injure tendons, and are responsible for much of what we now know about chronic tendinopathy [40,53,128,132,140], but are impractical as a model for most researchers, and, as is true for human tendinopathy, the amount (time and/or magnitude) of loading responsible for the tendinopathy is unknown. Animal models are now available that appear to simulate the type of overloading which often leads to human tendon dysfunction [77,78]. In one such model, the ankle joints of anesthetized rabbits were repeatedly flexed and extended for two hours daily while the triceps surae muscle was electrically stimulated. After four weeks of exercise, palpation of the exercised tendons showed that all had irregular thickening, with nodules a short distance from the tendon's insertion into the calcaneus. Light microscopy showed degenerative changes in the tendon and thickening of the paratenon [77]. Blood flow was increased (about two-fold) to both the paratenon and the tendon [78]. Cellular changes suggestive of an inflammatory response were found in the tendon sheath, with degenerative changes in the central portion of the tendon. This model first produced tendon dysfunction through reproducible loading, and has been subsequently modified by others [78].

The findings from human surgical and postmortem specimens, and from animal studies, suggest that most of the inflammatory changes take place in the paratenon and are accompanied by areas of focal degeneration within the tendon [77]. These findings also suggest that injury to the tendon structure does not occur in isolation, and that it would be uncommon for tendon degeneration to occur without some accompanying inflammatory changes around the tendon. In other words, it should be possible to have paratenonitis without tendinosis (as can occur with extrinsic tendinopathy), but not tendinosis without *some* inflammation of the tendon sheath at some point in time. Indeed, the presence of mild inflammatory changes may trigger or accelerate tendon degeneration [80].

It seems unlikely that tendon damage takes place without symptoms being present at some point, although these may be so minor that they escape notice. Patients may not complain of pain serious enough to prevent them from participating in activities they consider enjoyable (or unavoidable), but careful questioning will often reveal that symptoms were/are present during activities that load the tendon, or that a more acute episode did take place at some earlier time. Perhaps, these symptoms are so minor to be confused with ordinary post-exercise soreness. Tenderness on palpation and pain on loading, when present, may be interpreted to reflect the presence of an inflammatory response [138]. The response, even if it is primarily in the tendon sheath, somehow reflects the structural damage to the tendon, but the exact relationship is not yet known. The recent development of biopsy techniques for use in human and equine subjects seems a promising avenue for obtaining more accurate information about injured tendons [141,142].

Clinically, it is usually impossible to determine the exact source of pain, since palpation involves both the tendon and its sheath, and muscle contraction deforms both the inflamed sheath and the damaged tendon. We can therefore define tendinopathy as a syndrome of pain and tenderness localized over an area of tendon, aggravated by activities that apply force to the particular muscle-tendon unit. The syndrome can include inflammation of the tendon sheath, possibly inflammation of the tendon substance itself, and is either caused or followed by degenerative changes in tendon structure. Since it is unlikely that pathological changes can be determined for most patients, we use a classification system based on pain and function, which can be determined clinically, even though the exact relationship between symptoms and pathology remains unknown [143] (see Table 24-3). Other classification systems also show promise for establishing a systematic means of assessing the severity of chronic tendon problems [144,145].

General Principles for the Management of Tendinopathy

Many principles, physiological and mechanical, should be considered when treating chronic tendinopathy. Some of

Table 24-3. Classification of tendon disorders

Intensity	Level	Pain	Function
None	1	None	Normal
Mild	2	Minimal intensity With extreme exertiononly Ceases when activity Stops	Normal
	3	Moderate level During Activity Stays about same level Lasts 1–2 hours after onset	Normal or slightly decreased
Moderate	4	During activity Increases after onset Lasts 4–6 hrs after activity stops	Decreased
Severe	5	Starts as soon as tendon is loaded Rapidly increases Lasts 12–24 hours	Markedly or not able to participate
	6	During any tendon loading Pain may be continuous	Sports impossible Daily activities may be impaired.

the most important guidelines for treating tendinopathy, as outlined in Table 24-4, are:

1. Identify and remove all negative external forces/factors. In extrinsic tendinopathy, the outside force is usually pressure on the tendon. Identification and removal of the source of pressure is a fundamental step in the management of this form of tendinopathy, and is imperative if further tendon damage is to be avoided. All other forms of treatment, though helpful in relieving symptoms or restoring range of motion, can only be considered temporary or adjunctive. *Eliminating the cause is the fundamental treatment*.

Unfortunately, there is little evidence to support the role of external factors in causing, or contributing to, the treatment of chronic tendon injury [81]. Assessment and modification of such factors are usually part of an overall management package, making it difficult to ascertain the effectiveness of each part. This applies especially to what may be the single most common contributing factor in almost all cases of chronic tendinopathy—a lack of flexibility of the involved muscle-tendon unit [146]. Nonetheless, removal of external factors is relatively simple, costs little, and does no harm. It seems logical to deal with an apparent possible cause of the problem.

Table 24-4. Clinical principles for the management of chronic tendinopathy

Principle	Example
Identify and remove negative external factors	Shoulder hypomobility Foot pronation Lack of flexibility Compression of tendon
Estimate phase of healing or degree of tissue injury	Severe pain = acute injury Swelling = tendinopathy Tenderness = tendinopathy
Determine focus for initial treatment	Severe = pain control and healing Mild, moderate = progressive loading
Institute appropriate tensile loading program	Acute = low force Chronic = enough load to produce symptoms
Control pain and inflammation	Severe = drugs, modalities Mild, moderate = ice

2. Estimate the phase of healing (stage of tendinopathy). This is a very imprecise process, and requires clinical judgment based on the examiner's clinical experience. Table 24-3 can be used as a guide for those unfamiliar with staging chronic tendinopathy. Generally, the more severe the patient's symptoms, the more closely the choice and timing of loading should resemble that used for an acute-onset tendon injury. Treatment should also progress as it would for an acute injury.

3. Determine the appropriate focus for initial treatment. This involves matching treatment with the stage of healing. Most patients with chronic tendinopathy are probably in the remodeling phase of healing, where force application is most effective. More severe cases may have to be initially treated with relative rest (reduced loading), ice, and modalities for a short period of time, perhaps 10 to 14 days. These injuries may be more appropriately considered acute injuries, at least based on signs and symptoms, and managed accordingly. This should be followed by gradual stress increase, as is the case for an acute tendon injury or repair.

4. Institute an appropriate tensile loading program. The healing tendon must be loaded if collagen synthesis, alignment, and maturation via crosslinking are to be ideal. The more acute or severe the injury (indicated by knowledge of the injury or the degree of symptoms), the lower the force that should be applied. Passive movement produces very little tensile force, is safe immediately after

injury, and exerts beneficial mechanical effects on tendon. Gentle stretching would be the next step, followed by increased stretching force and then active exercise (see Figure 24-7).

5. Control pain

Inflammation (at least as it is traditionally considered) does not seem to play a role in chronic tendon injuries. There is little evidence of the effectiveness of nonsteroidal anti-inflammatory drugs in the management of chronic tendinopathy, but it has been suggested that they may be useful in the very early stages (2 to 3 days) of tendon dysfunction [81,147]. Judicious use of loading during healing should ensure that mechanical disruption and reinjury, perhaps provoking an inflammatory response, do not occur. Clinical signs and symptoms consistent with an inflammatory response (pain, swelling, tenderness) may suggest that additional measures are required to reduce a prolonged inflammatory response. Drugs, ice, and modalities can be used as adjuncts to treatment according to the practitioner's background and clinical experience. In such cases, it is essential that any reduction in symptoms not change the original plan for loading progression. Elimination of pain could allow "overloading" of the tendon, and a rebounding or worsening of symptoms once drug use is discontinued. Since pain is the means by which appropriate loading intensity is monitored, the use of pain-relieving agents should be avoided unless the patient's functional level makes their use necessary. During the period of administration of pain-relieving agents, patients should be treated as if they had an acute partial tendon rupture. Once pain is eliminated, the agent can be withdrawn, and a progressive loading program can begin.

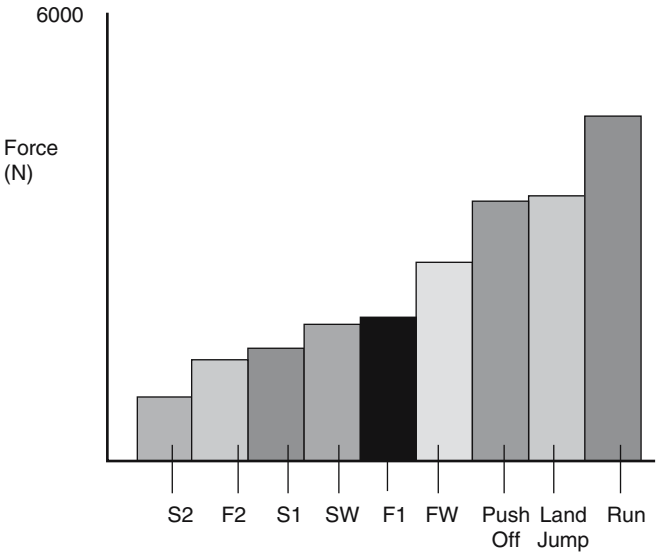

FIGURE 24-7. Sample loading progression for chronic tendinopathy. Once the tendon can be actively exercised, the load must be continually progressed. The principles described later in this chapter, and illustrated in Figures 24-9 to 24-11, should be followed. In this example, the loads on the Achilles tendon of one female subject were estimated for different stages in the eccentric exercise program using the calculation method shown in Figure 24-2. Note that the highest stage in the exercise program did not generate forces as large as those observed during running [8].

Specific Forms of Treatment

Modalities

Physical therapists employ a wide variety of modalities in treating soft tissue disorders, including: ultrasound, laser, ice, heat, pulsed electromagnetic current, electromagnetic field therapy, high-voltage galvanic stimulation, acupuncture, interferential current, etc. Most are thought to "decrease inflammation and promote healing." Unfortunately there is only limited evidence as yet to support many of these claims.

Ultrasound is one of the most commonly used modalities. Generally, pulsed ultrasound is recommended for acute injuries, to avoid a thermal effect, and continuous ultrasound is used for more long-standing injuries [148,149]. In some investigations, ultrasound produced no influence on healing tendon [150], while other studies showed that ultrasound increased collagen synthesis by fibroblasts [151], speeded wound healing [148,149], and resulted in increased tensile strength in healing tendons [152]. Ultrasound has little or no effect on inflammation [153]. None of the experimental models used in these studies simulated the clinical situation of chronic tendinopathy, so one can only assume that the chronically injured tendon heals in a manner similar to the severed tendon. It is not clear whether the normal healing process occurs in chronic tendinopathy, so this assumption is doubtful. Ultrasound probably has its most important effects when the synthetic activity of the fibroblasts is at maximum, i.e. during the proliferative stage of healing, but, because of the long-standing nature of chronic injuries, it may actually be most widely used clinically during the remodeling stage. It would be interesting to ascertain whether ultrasound increases the synthesis of collagen during all stages of healing, especially during remodeling, when the cellular synthesis rate has declined. Stimulation of synthetic activity appears to be ultrasound's most likely means of "promoting healing," and would, in effect, prolong the proliferative phase of healing. Given the timing of the normal healing response, with the relatively short duration of enhanced cellular synthetic activity, there would seem to be little indication for using ultrasound beyond 2 to 3 weeks at most. Recent systematic reviews of

the use of ultrasound to treat soft tissue injuries showed little evidence of efficacy except in the treatment of calcific tendinopathy and lateral epicondylitis [154,155].

Electrical stimulation has a positive influence on tendon healing [156,157]. Again, results were obtained from acute tendon healing models and may not necessarily represent chronic tendon injuries. Both direct electrical stimulation [156,157] and indirect current via electromagnetic field induction [158] seem to augment tendon healing. Pulsed electromagnetic fields can treat both deep and superficial tissues, and cover larger areas than ultrasound or laser [159]. Questions about timing and dosage remain unclear, but this treatment may to be prolonged for several hours daily to have an influence on the tissue, since clinical use for shorter periods of time has not shown the same positive effects [160].

One of the most widely used modalities for all soft tissue injuries is *ice*. Its use is recommended immediately after injury to prevent excessive soft tissue swelling, and it probably acts mainly by decreasing the activity of inflammatory mediators and decreasing the overall metabolic rate of the injured tissue [161]. Another important effect is analgesia, which allows the use of appropriate forms of exercise, such as passive motion, that otherwise might be uncomfortable for the patient. The use of ice with chronic injuries is less clear, although it can be used for its analgesic effect, and may help offset changes induced by mechanical injury to the tendon during exercise [162].

The use of modalities, although widespread, remains largely speculative and scientifically untested in the management of chronic soft tissue injuries. Most studies suggest that increased synthetic activity by fibroblasts is the major effect of most modalities, except ice. Clinicians should always keep in mind that this synthetic activity is mainly part of the proliferative phase of healing, and that mechanical forces are also required during remodeling if the newly synthesized collagen is to assemble and crosslink into a structure capable of withstanding tensile loading. The effects of modalities on chronic injuries remains largely unexplored, and well-designed clinical trials are needed to determine efficacy in the clinical setting [1,155].

The failure of many patients' tendinopathy to respond to conventional nonsurgical treatment, and a growing appreciation for tendon physiology and mechanics, suggest that a modality-centered approach to the treatment of chronic tendinopathy is inadequate. Modalities need not be abandoned altogether, but they should not form the basis of a treatment strategy for chronic tendinopathy. At best, this will afford a temporary relief of symptoms, and at worst create dependency on the clinician and inflate health care costs. An understanding of tendon's ability to adapt to increased loads, and the belief that chronic tendon injuries are the result of tensile loads exceeding the tendon's mechanical strength, suggest that exercise should be the cornerstone of treatment.

Drugs

The most potent anti-inflammatory drugs are the corticosteroids, which are sometimes used, via local injection, to manage chronic tendinopathy. The negative effects of systemic corticosteroid use are well known [112,113], but the effects of local injection are less clear. Both negative and no effects have been reported [163,164]. However, it seems generally agreed that injection into the tendon substance should be avoided. This is due to the effects of the drug (which decreases collagen synthesis), the mechanical disruption caused by the needle, and the irritant effect of the solvent in which the drug is dissolved. Given the potent anti-inflammatory effect, and the fact that most inflammatory changes occur in the paratenon, injection into the tendon sheath and paratenon may be indicated if symptoms are marked or prolonged [164]. Once the injection has been administered, the tendon should be treated as a partial rupture. Tensile stresses should be reduced for 10 to 14 days, and the tendon treated with ice, rest, modalities, followed by progressive loading. Repeated steroid injections should be avoided [163].

Nonsteroidal anti-inflammatory agents (NSAIDs) are also widely used in the management of acute soft tissue injuries, and less so for chronic injuries such as tendinopathy. They are thought to limit inflammation by inhibiting prostaglandin synthesis, although other mechanisms are also involved [166,167]. While there is some evidence to show that preventive use of indomethacin may reduce subsequent muscle injury, most clinical studies have had design flaws, making it impossible to conclude whether the use of NSAIDs has a beneficial effect on postinjury recovery [164,165]. It is important to identify exactly what drugs the patient is taking, since many of these agents may be self-administered, and an anti-inflammatory action may be assumed when only an analgesic effect is actually present.

Some patients may also be self-administering another class of drugs known to affect connective tissues, anabolic steroids. While the exact effects of these agents are unknown due to difficulties in determining use and dosage, there is both scientific and anecdotal evidence to suggest that anabolic steroid users are more likely to develop a tendon injury [168]. The effect of anabolic steroids on the healing of chronic tendon injuries is unknown.

Surgery

Surgery should be used only if conservative measures have failed, unless the tendon ruptures and the ends need to be approximated [169,170]. Other chapters in the

present book deal specifically with surgery of tendon ailments.

Exercise in the Treatment of Tendinopathy

Treating Acute Tendon Injuries Using Exercise

The guide to treating the severed tendon has been well established (Table 24-2). The main aims are to prevent tissue disruption while minimizing the negative effects of disuse on other parts of the musculoskeletal and cardiorespiratory systems. The recovering tendon is subjected to progressively increasing forces to enhance collagen fibril alignment, improve tensile strength, encourage continued fibroblast synthetic activity, and prevent adhesions between the healing tendon and adjacent tissues. Table 24-2 provides a framework on which to base all tendon injury rehabilitation, and can be readily applied to cases of tendinopathy where the exact time of injury is known.

Treating Chronic Tendinopathy Using Exercise

In contrast to the relative simplicity of the acute tendon injury, in which the onset of the tissue damage is known and the phase of healing can be estimated, when dealing with chronic tendinopathy we do not know the date of the initial injury, and it is difficult to decide where in the healing process the tendon lies. There are no accurate means of assessing human soft tissue injuries such as tendinopathy, although several techniques such as ultrasound, magnetic resonance imaging, thermography, and biopsy show promise [141,171,172]. Even in acute tendinopathy, we cannot be certain about the degree of injury.

Since our understanding of chronic tendinopathy is inadequate, we are forced to make some assumptions on which to base treatment. The main assumption is that *the level of pain and dysfunction experienced by the patient is a reflection of the degree of injury to the tendon*. Thus, if pain increases, tendon damage is increasing. Pain is used to titrate the amount of load applied to the tendon; as pain decreases, load is increased. There is no direct evidence to support this view, as it is based on trial and error [143]. Some authors have successfully used heavy loading exercise to treat tendinopathy without basing progression on patient discomfort, suggesting that such careful attention to pain may not be necessary with all patients [173]. Since the source and mechanism of tendon pain remain unknown [139], its use as an indicator for treatment is empirical. Glutamate levels remain unaltered after tendon dysfunction has resolved, so its role in pain production is uncertain [174].

Basic Principles of Exercise

Basic exercise principles must be followed for any exercise program to succeed, whether its aim is to strengthen muscle or tendon. For the treatment of chronic tendinopathy, these are most important:

1. Specificity of training.
Training must be structure, load, and movement specific. The correct muscle-tendon unit must be loaded, it must be loaded in a way that produces controlled tensile loading, and the motor pattern should resemble the patient's activity. The exercise should, eventually, closely simulate the pattern of loading during functional activity in the *type* of loading (tensile, eccentric) and the *magnitude* and *speed* of loading. Specificity is achieved by simulating the movement pattern associated with maximal tendon forces, i.e. a lengthening of the active muscle-tendon unit followed by shortening contraction. The initial magnitude and speed of loading are based on the estimated stage of healing. The more acute the injury, the lower the force, and the slower the eccentric loading. The affected tendon must be subjected to specific, controlled tensile loading, not just a generalized exercise involving use of the affected muscle-tendon unit. The Achilles tendon, for example, is loaded by having the patients stand at the edge of a step and drop their heels downward, rather than running, even though the latter creates large loads on the Achilles tendon (see Figure 24-8). The patellar tendon can be loaded via squat-type exercises, while the wrist extensors can be loaded via wrist flexion/extension [143]. The aim of such specific loading is to isolate the mechanical effects of the exercise on the tendon from any potentially negative effects associated with stressful training.

2. Maximal loading.
Maximal loading is essential to induce adaptation in musculoskeletal tissues. In the case of an injured tendon, maximal loading can be defined as the force the tendon can withstand without further injury. Clinically, the maximum load applied is determined by the tendon's tolerance, which is judged by the patient's pain level during exercise. The patient should experience pain during the last 10 repetitions of 3 sets of 10 repetitions of the chosen exercise. We determined empirically that the most rapid and consistent improvement occurred if the patient experienced pain between the 20th and 30th repetition of the specific loading movement [143,175]. Pain before this point (<20 repetitions) was usually accompanied by overall worsening of the patient's condition, and this

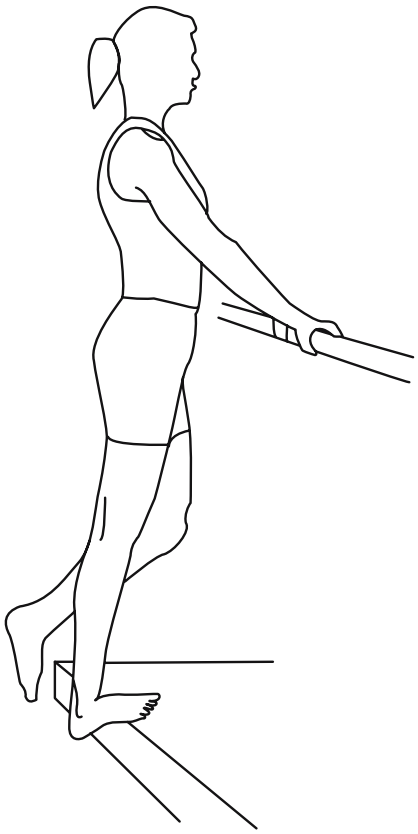

FIGURE 24-8. Exercise methods for eccentric loading. The Achilles tendon is loaded by having the subject stand at the edge of a step or support and allow the heel to drop over the edge. It is recommended that a support be used (or at least available) for balance. The progression of loading follows the sequence shown in Figure 24-10. See also Figure 24-7 for an illustration of the loads for one subject during eccentric loading of the Achilles tendon. Other tendons can be loaded in a similar manner.

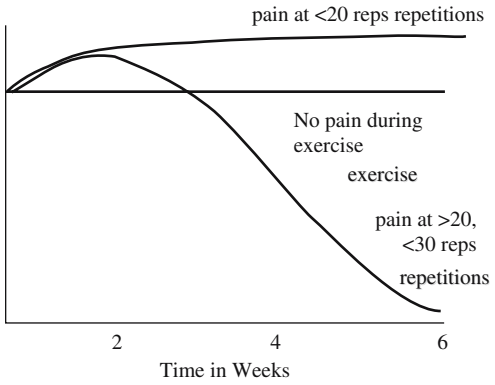

FIGURE 24-9. Time course of symptoms. The subject should experience pain after 20 repetitions; this pain will often increase in severity, but should not prevent the subject from finishing 30 repetitions of the exercise. If no pain is felt during 30 repetitions, no further progress occurs, and the patient will remain at his or her current functional level. In such cases, increase the external load or the speed of the exercise (not both). If pain is felt before 20 repetitions, especially if this increases rapidly with subsequent repetitions, the exercise load is too large and should be reduced. (Reprinted with permission from: Curwin SL. The aetiology and treatment of tendonitis. Ch. 4.4.4 in *Oxford Textbook of Sports Medicine*, 2nd Ed., Harries M, Williams C, Stanish WD, Micheli LJ (eds.), Oxford University Press, Oxford, 1998, Figure 13, pg. 624; Ref. 82.)

indicated overloading. Patients who experienced no pain or discomfort during the 30 repetitions, yet who continued to have symptoms during functional activities, did not see any change in overall status (see Figure 24-9). We suggested that the loading stimulus was inadequate to induce a change in the tendon, and recommended that loading be increased to induce further adaptation [143,175].

3. Progression of loading.

As the tendon becomes stronger, loading must be progressed so that maximal loads continue to be applied and the tissue will continue to have a stimulus for adaptation. This progress can be made by increasing the speed of movement or by increasing the magnitude of the tensile force through changing the external resistance (see Figure 24-10).

The overall progression of loading is determined by the patient's symptoms, as described above, so that a

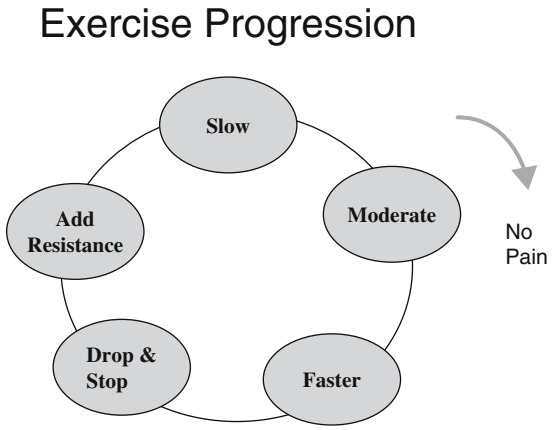

FIGURE 24-10. Changing tensile loading in the eccentric exercise program. The load on the tendon can be increased by changing the external load (e.g. shifting from two foot support to one foot support) or by increasing the speed of the movement. The fastest speed is the "drop & stop" – a sudden stopping of downward movement that creates the simultaneous occurrence of maximum stress and strain on the tendon.

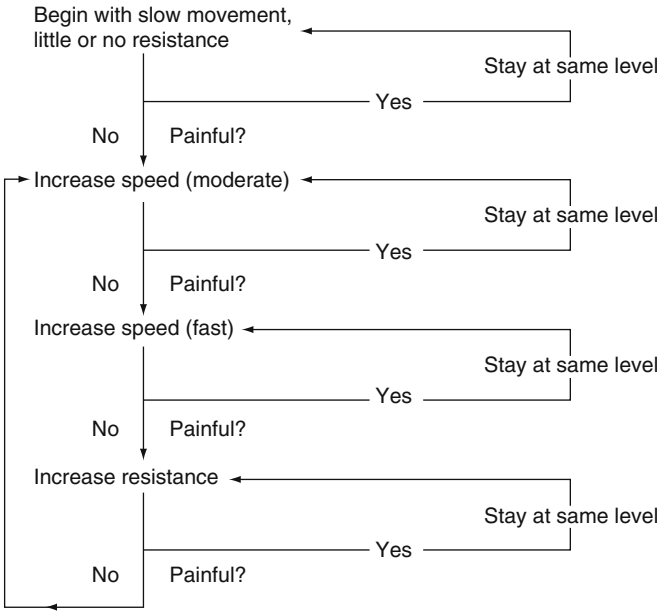

FIGURE 24-11. Eccentric exercise program flowchart. This flowchart illustrates the sequence of progression for Achilles or patellar tendinopathy. Each step takes 5 to 7 days.

maximum load is always applied (see Figure 24-11). As soon as 30 repetitions can be performed without discomfort, the tensile force is increased.

Eccentric Exercise Program

The regular use of resisted exercise as a treatment for chronic tendinopathy (tennis elbow) has long been recommended [117]. The principles outlined above also have been incorporated into an "eccentric exercise program" for treating chronic tendinopathy. This program was developed in the early 1980s by a physiotherapist (Sandra Curwin), an orthopedic surgeon (William Stanish), and a medical student with an MSc in Biomechanics (Howard Lamb), in response to the frustration of unsuccessfully treating patients with chronic tendon injuries [143,175]. The basic program design can be applied to any injured tendon. The overall program has five steps, which are performed in the order listed, and summarized in Figure 24-12:

1. Warm-Up

A generalized exercise like cycling or light jogging is used to increase body temperature and increase circulation. This exercise is not intended to load the tendon and should not be uncomfortable.

2. Flexibility

Lack of flexibility is common in patients with chronic tendinopathy [145]. Patients should perform at least two 30-second static stretches of the involved muscle-tendon unit and its antagonist. More stretching may be performed if this is felt to be a major factor in causing the patient's symptoms, i.e. the patient's range of motion is restricted by muscle shortening. Since two-joint muscles are most often involved, it is important that range of motion be examined at both joints simultaneously.

3. Specific Exercise

This is done following the guidelines in Figure 24-10, based on the principles outlined above. It is suggested that three sets of 10 repetitions be performed, with a brief rest, and sometimes a stretch, between each set. The patient should feel a reproduction of his or her symptoms after 20 repetitions. If pain is felt earlier, reduce the speed of movement, or decrease the load (decreases the load on the tendon); if no pain is experienced, increase speed *or* load (increases the load on the tendon). If this is the first exercise session, and the initial level of loading is being determined, the intensity of exercise may be increased, and the 30 repetitions repeated until the appropriate level of intensity is reached. Load or speed can then be adjusted at the next session, based on where pain occurs during the 30 repetitions.

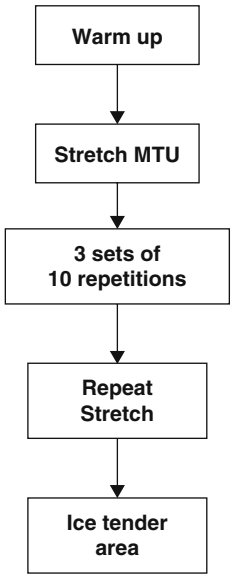

FIGURE 24-12. Summary of steps in the eccentric exercise program.

4. Repeat Flexibility Exercises

5. Apply Ice

Ice is applied for 10 to 15 minutes to the affected (painful to palpation) area. This may help prevent the inflammatory response provoked by microscopic damage to the tendon that might occur during the exercise. As the presence of inflammation is debatable, this step may be unnecessary. The above steps are summarized in Figure 24-12.

Since this program is designed for patients with chronic tendinopathy, most people are able to continue to participate in athletic (or other) activity, but may find participation painful and/or their performance impaired. Patients will need to use their own judgment to determine whether or not to participate, but in general, *patients do not need to cease participating in sports unless they are unable to perform adequately*. Indeed, it is best if patients change nothing about their activity *except* adding the exercise program (the independent variable), since this makes it much easier to assess the effect of the exercise on the tendon. A decrease in physical activity is almost always accompanied by a parallel decrease in symptoms. Hence, if patients cease activity participation, it makes the success of the exercise (or any other treatment) difficult to assess, since multiple factors are changing at the same time. Ideally, the environment and activities will remain the same, and the clinician will change only one variable at a time, evaluating its effect before moving to the next intervention. The outcome measures (dependent variables) are level of function and pain during activity, or some other measure of chronic tendon dysfunction, e.g. grip strength in lateral epicondylitis [144–147]. Only one intervention, exercise, is necessary for most patients — other interventions are adjunctive to the loading program. The exercise program can take 6 to 12 weeks (or longer) to achieve positive results, and the clinician and patient must be prepared to devote at least this period of time to assess the outcome of the program. The exercises are performed daily, with continuous progression following the flowchart in Figure 11, *until symptoms are no longer present during functional activity (no activity limitations)*. By this time the patient should be fully recovered and able to perform all functional activities with little or no pain (i.e. no participation restriction).

The cost of using exercise as a treatment for chronic tendinopathy is minimal. It is not necessary for patients to be treated one-on-one by the physical therapist after the appropriate starting point for the exercise program has been established, which usually takes two visits. Patients can often be successfully treated with a thorough explanation of the exercise program, independent performance of the exercise program and periodic rechecks/progression in person or by telephone. Most patients will have recovered in 6 to 12 weeks. Telephone or e-mail rechecks are convenient and inexpensive, and allow the clinician to monitor the patient's level of exercise and functional performance. If no change has occurred, symptoms have worsened, or noncompliance is suspected, an appointment can be made. A typical overall pattern of visits might be distributed something like this:

1. Differential diagnosis and start exercise program. Give patient exercise instructions and recording sheet.
2. Check for correct performance of exercise. Adjust exercise program so patient has pain between 20 to 30 repetitions
3. Recheck after 2 weeks on program.
4. Recheck after 4 weeks on program.
5. Recheck after 6 weeks on program; discharge if symptom-free.
6. Recheck after 8 weeks on program; discharge if symptom-free.

Program progression can be monitored in several ways: 1) objectively via the amount of force applied to the affected limb and/or the speed of movement; 2) subjectively via the patient's report of pain after specific exercises or activities; and 3) functionally via the patient's ability to successfully perform those activities considered normal for him or her (e.g. basketball lay-up, 1 hour of tennis, run 5 miles, etc.). Maximal strength testing, especially using an isokinetic device, should *not* be performed until after treatment is completed and the patient is asymptomatic. The maximum force levels generated during such testing, especially isokinetic eccentric testing, are likely to damage the healing tendon and will often exacerbate symptoms. While program progression and success are based almost entirely on subjective assessment of symptoms by the patient, strength deficits may exist in some tendinopathy patients even after symptoms are gone. Thus, strength testing may be useful after completion of the rehabilitation program to determine what type of follow-up intervention might be recommended [176]. It is not known whether these strength changes helped cause the tendinopathy, or are the sequelae of decreased use due to tendon dysfunction.

Modification of functional activity probably will be necessary if patients have severe or constant pain. Most of these patients will have already reduced their activity level, and this reduction in performance is the most likely reason for patients' seeking professional attention. This level of pain may be interpreted as reflecting an ongoing process of acute tendinopathy, even though symptoms may have been present for weeks or months, and treatment should begin at a very low level of loading intensity: ice, gentle stretching, passive movement, modalities to stimulate collagen synthesis, etc. Treatment is changed as healing progresses, so that, by 2 weeks, more vigorous exercise can usually be introduced as the patient's symp-

toms will have subsided. Overall treatment will be extended by the time period needed to control the acute symptoms and get the patient to a level where pain is present only during/after activity.

For patients who have curtailed their functional activities, returning to full activity creates a delicate balancing act for the patient and clinician. For patients who continued sports participation throughout the treatment period, this generally is not a problem. Patients with more severe tendinopathy, who limited their functional activities, must adopt a gradual approach to resuming activity. There are no rules to guide re-introduction to activity, but the patient should be asymptomatic during nonathletic activities and should be performing the eccentric exercise program rapidly. Athletic involvement can be started at about 25% of the pre-injury level (duration or intensity, depending on the sport and movement), and should be undertaken on alternate days to avoid muscle soreness, and to allow evaluation of the tendon's response to training. Assuming that few or no symptoms are present, progression can be made in approximately 10% to 20% increments, monitoring symptoms, until full training has been resumed. This should take about eight weeks, making the entire treatment period for a patient with severe tendinopathy a maximum of 14 weeks. If pain recurs during activity, or increases in intensity, the patient should drop back to the prior training level, after a short rest period (1 to 2 days). Most patients will require at least six weeks of treatment, a few will experience complete resolution in 2 to 3 weeks, and very few others will need to continue for 12 to 16 weeks (see Figure 24-13).

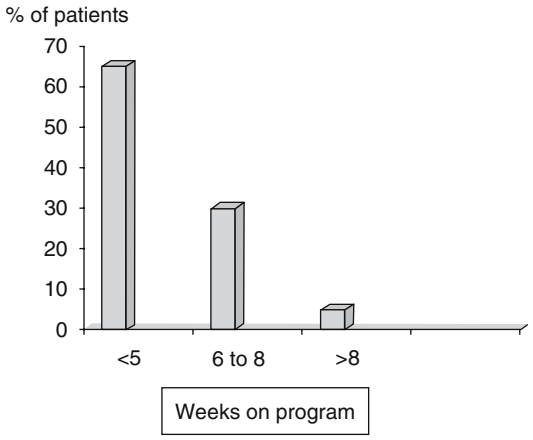

FIGURE 24-13. Timeframe for recovery with the eccentric exercise program. The time course of recovery (complete recovery or marked relief of symptoms and return to full activity) for 200 patients using the eccentric exercise program. Most people spent less than 6 weeks on the program, a few spent more than 8 weeks [142].

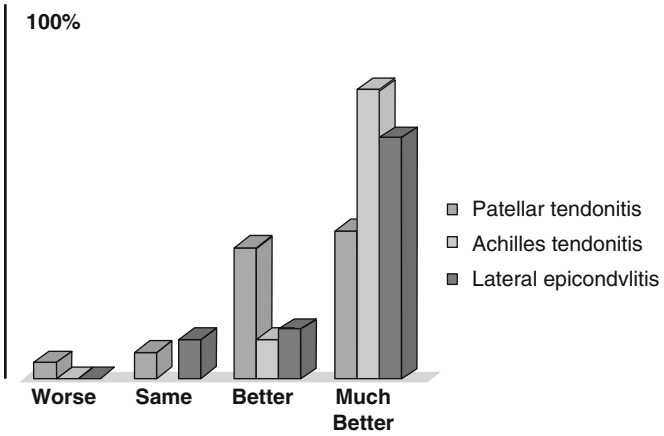

FIGURE 24-14. Patient response to the eccentric exercise program. Shows the percentage of 200 patients with Achilles tendinopathy, patellar tendinopathy or lateral epicondylitis who experienced complete relief or marked relief (full function, minimal pain) of symptoms after 6 weeks on the eccentric exercise program [142].

Success or Failure of the Program

Curwin and Stanish designed the eccentric exercise program in response to the large numbers of patients with chronic tendinopathy who were referred to them after the failure of conventional treatment. After designing the eccentric program, creating an estimate of tendinopathy severity, and empirically determining program progression, they monitored 200 chronic tendinopathy patients treated using the program. Most had minimal or no symptoms after 6 weeks [143] (see Figures 24-13 and 24-14). These patients had all been treated previously with modality-based therapies, some several times, and the average duration of symptoms was 18 months, with a range of 6 months to 10 years. Many came from far away, and were unable to be seen on a daily or near-daily basis. Of these patients, 85% had moderate or severe tendinopathy (i.e. pain hindering or preventing performance). All patients had received various prior treatments for tendinopathy, some up to 6 separate times. The ideal treatment needed to be something based on exercise science, but able to be completed independently by the patient, at a low cost. The eccentric exercise program met these criteria [143]. The results from the 200 patients showed that about 90% of them experienced marked or complete relief of symptoms.

Curwin and Stanish had a large series of patients, but did not use a control group, nor did we randomly assign patients to different treatment interventions, largely due to their patients' refusal to accept other forms of treatment that they had already tried without success. This

limits the scientific validity of our findings, which were described in two books and several publications [143,174, 177,178]. Since these initial descriptions, however, the eccentric program has been widely used clinically and better-designed studies have been performed, and the program is now recommended as a treatment for chronic tendinopathy [81,178–193].

Several groups have subsequently examined the efficacy of the eccentric exercise program in treating Achilles tendinopathy, patellar tendinopathy, and lateral epicondylitis [181–193]. All have found the program to be effective, although the eccentric loading is sometimes slightly different from that suggested here. Alfredson [173], for example, used heavy eccentric exercise to treat Achilles tendinopathy, without accounting for pain, and obtained excellent results in about 85% of patients. This runs counter to our experience that careful attention to the level of pain is crucial for improvement. We have found that a high level of pain, or pain too early in the program (before 20 repetitions) can cause a worsening of symptoms, while no pain during exercise results in patient stasis [142,172] (see also Figure 24-9). Whether this careful attention to pain is really necessary requires further examination.

Modalities can also be employed if desired, especially if the patient's symptoms are acute or prolonged and the clinician suspects that the synthetic activity of the tendon is decreased, but should not be the only treatment used. Similarly, the physician may decide to use NSAIDs if the inflammatory phase is prolonged. The use of such agents will make it more difficult to assess program efficacy, but the clinician must use his or her clinical judgment as to what will work best for a particular patient.

If the Exercise Program is Not Successful

Findings to date suggest that 85% to 90% of patients using the eccentric exercise program will experience marked or complete relief of chronic tendon dysfunction within 6 to 14 weeks [143,181–193]. If the eccentric exercise is not successful in treating the patient's tendinopathy, several explanations are possible:

1. Incorrect Loading Magnitude or Progression

A slight increase in symptoms at the beginning of the program should not be viewed with alarm. In fact, this simply confirms that this is a load-related problem. Any increase in pain should be temporary. Slightly reduce the magnitude of loading, have the patient avoid doing the exercise program immediately before or after athletic activity, and encourage the use of ice after exercise and activity. For exercise treatment to be successful, symptoms *must* be related to tensile loading, usually during eccentric muscle activation (symptoms may not be provoked by concentric or isometric testing). The most common reason for lack of success is incorrect program progression (see also Figure 24-9). The patient is either started at too high a level—and gets worse—or is not progressed to the next level of intensity—and stays the same. A progressive increase in symptoms indicates that an inappropriate level of loading has been chosen, or the patient is performing the exercise incorrectly. Depending on the level of symptoms, the tendinopathy may now need to be treated as an acute injury. Little ground is lost if the patient understands the meaning of increased symptoms, or the therapist immediately adjusts the treatment intensity.

2. Incorrect Diagnosis

Should 2 weeks of patient-directed, or 1 week of clinician-directed (2 to 3 treatments) pass without any improvement or ability to progress the load on the tendon, the clinician should thoroughly reevaluate the patient and reconsider his or her diagnosis. If he or she remains convinced that tensile loading is the cause (and the solution), the loading program will need to be adjusted. The patient may not have tendinopathy, or there may be unrecognized external factors that are causing or perpetuating the problem. A thorough check of spinal and peripheral joint range of motion (active, passive, and accessory), alignment, flexibility, and resisted movements is required to search for one or more maneuvers that will reproduce the patient's symptoms [125,126]. Such a sign or signs also can be invaluable in evaluating patient response to treatment. As a rule, if abnormal joint signs are found, these should be treated first [126]. Failure to respond to treatment after elimination of possible outside factors should make the clinician suspicious about systemic disease, overtraining, or hormonal or nutritional imbalance [74,85,88,116,122]. These alternative explanations for tendinopathy-like symptoms are not common in athletes, but should be considered [114].

Summary

Chronic tendinopathy remains a clinical dilemma. The best treatment is not always possible or recognized, or the patient may be unable to follow the ideal treatment strategy because of recreational or work-related demands. An ideal treatment will resolve the current symptoms and prevent their return, and should be based on good science, common sense, and clinical results. The use of exercise to treat chronic tendinopathy began with a knowledge of tendon loading during activity, the science of tendon adaptation to increased stress, and the common sense of patient participation based on ability to perform. There now is a growing body of evidence suggesting that

eccentric exercise is successful in treating chronic tendinopathy, but most of these studies suffer from many of the same limitations of other clinical studies—small numbers, lack of randomization, lack of a control group, lack of a uniform diagnostic system, lack of agreement on outcome assessment, and so on. The literature suggests that chronic tendinopathy may persist if untreated [93,169,187], but the natural history of chronic tendinopathy is still not clear [93,175]. Exercise alone will not solve all cases of tendinopathy. Clinical judgment is essential, and a careful analysis and systematic elimination of many other factors is often involved. Once these influences have been removed, knowledge of the adaptation of tendon in response to tensile loading can be used to successfully manage most tendon injuries.

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25
Surgery for Chronic Overuse Tendon Problems in Athletes

Nicola Maffulli, Per Renström, and Wayne B. Leadbetter

Tendon disorders are a major problem in sports and occupational medicine. Tendons have a high tensile strength thanks to a high proportion of collagen in their fibers and a closely packed parallel arrangement in the direction of force [1]. The individual collagen fibrils are arranged into fascicles which contain blood vessels, nerve fibers and lymph. Specialized fibroblasts, tenocytes, lie within these fascicles, and exhibit high structural organization [2]. At histology, tenocytes appear as star shaped cells in cross sections. In longitudinal sections, they are arranged in rows following the direction of the tendon fibers. This specialized arrangement is related to their function, as tenocytes synthesize both fibrillar and nonfibrillar components of the extracellular matrix, and are able to reabsorb collagen fibrils [3]. The fascicles themselves are enclosed by epitenon, which is surrounded by the paratenon, and the potential space between them is filled by a thin, lubricating film of fluid which allows gliding of the tendon during motion.

The pathologic label "tendinosis" has been in use for more than 2 decades to describe collagen degeneration in tendinopathy [4]. Despite that, many clinicians still use the term "tendinitis," thus implying that the fundamental problem is inflammatory [5]. We advocate the use of the term *tendinopathy* as a generic descriptor of the clinical conditions in and around tendons arising from overuse [6,7]. The terms tendinosis and tendinitis should be used after histopathological examination [8].

Tendinosis is defined [1] as intratendinous degeneration (i.e. hypoxic, mucoid or myxoid, hyaline, fatty, fibrinoid, calcific or some combination of these), due to a variety of causes (aging, microtrauma, vascular compromise, etc.). Histologically, there is noninflammatory intratendinous collagen degeneration with fiber disorientation and thinning, hypercellularity, scattered vascular ingrowth, and increased interfibrillar glycosaminoglycans [1,6,9–11]. Tendinosis is a failure of cell matrix adaptation to trauma due to an imbalance between matrix degeneration and synthesis [5,10]. Macroscopically, the affected portions of the tendon lose their normal glistening white appearance and become gray and amorphous. The thickening can be diffuse, fusiform or nodular [12].

The paratenon can be involved in the early phases of tendinopathy, and may present as "peritendinitis crepitans" due to adhesion between the tendon and the paratenon. Histologically, tendinosis shows partial disruption in tendon fibers. Tendinosis can be asymptomatic: for example, most patients with an Achilles tendon rupture did not have a clinical picture of tendinopathy before the rupture, and only histology reveals the profound intra-tendinous changes. Tendinosis may also coexist with symptomatic paratendinopathy [5,13].

Pain in Tendinopathy

Four types of nerve endings can normally be identified in tendons. The Ruffini corpuscles, free nerve endings, Pacini corpuscles mainly at the tendon site and the Golgi tendon organs mainly at the muscular site [14]. The source of pain in tendinopathy is still under investigation. Classically, pain was attributed to inflammatory processes, but, as it has become evident that tendinopathies are degenerative, not inflammatory conditions, recently the combination of mechanical and biochemical causes has become more attractive [15,16]. Tendon degeneration with mechanical breakdown of collagen could theoretically explain the pain mechanism, but clinical and surgical observations challenge this view [16]. The biochemical model has become appealing, as many chemical irritant and neurotransmitters may generate pain in tendinopathy. High concentrations of the neurotransmitter glutamate in patients with Achilles tendinopathy have recently been found [17]. The tendons in these patients showed no signs of inflammation, as indicated by the normal prostaglandin E2 levels [17]. Substance P and chondroitin sulphate may also be involved in producing pain in tendinopathy [15].

Complete or modified rest from sport, non-steroidal anti-inflammatory drugs, cryotherapy, deep frictional massage, ultrasound therapy, pulsed electro-magnetic fields, laser therapy, orthoses, and eccentric exercises [18,19] have all been described in the management of tendinopathy, together with local peritendinous injections of steroids or aprotinin [2]. If these measures fail, surgery is an option [15,16,20]. In the absence of frank tears, the traditional operation involves a longitudinal skin incision over the tendon [21,22], paratenon incision and stripping, multiple longitudinal tenotomies, and, if a definite area of degeneration is found, its excision [15,16,23]. Surgery aims to promote wound repair induced by a modulation of the tendon cell-matrix environment [20], but even in very experienced surgeons the rate of complications can be high [24,25], and success is not guaranteed [26].

Treatment of chronic tendinopathy aims to allow patients to return to normal level of physical activity [15,16,20]. Percutaneous needling of the tendon for such purpose has been recently reported, even though no results have been published [20], and open longitudinal tenotomy has been long established [15,16,23].

Biology of Tendon Healing

Tendon healing is classically considered to occur through extrinsic and intrinsic healing. The intrinsic model produces obliteration of the tendon and its tendon sheath. Healing of the defect involves 2 phases, an exudative and a formative phase which, on the whole, are very similar to those associated with skin wound healing [27]. Extrinsic healing occurs through the migration of tenocytes into the defect from the ends of the tendon sheath [28]. This process classically occurs in 3 phases: inflammation, repair, and organization or remodeling. In the inflammatory phase, 3 to 7 days after the injury, cells migrate from the extrinsic peritendinous tissue such as the tendon sheath, periosteum, subcutaneous tissue and fascicles, as well as from the epitenon and endotenon [29]. Initially, the extrinsic response, which far outweighs the intrinsic one, results in rapid filling of the defect with granulation tissue, tissue debris and hematoma. The migrating tenocytes play a phagocytic role, and are arranged in a radial fashion in relation to the direction of the fibers of the tendon [2]. Biomechanical stability is given by fibrin.

The migrated tenocytes begin to synthesize collagen around day 5. Initially, these collagen fibers are randomly orientated. Tenocytes become the main cell type, and over the next 5 weeks collagen is continuously synthesized. During the fourth week, a noticeable increase in proliferation of tenocytes of intrinsic origin, mainly from the endotenon, takes place. These cells take over the main role in the healing process, and both synthesize and reabsorb collagen. The newly formed tissue starts to mature, and the collagen fibers are increasingly orientated along the direction of force through the tendon. This phase of repair continues for some 8 weeks after the initial injury. Final stability is acquired during the remodeling induced by the normal physiological use of the tendon. This further orientates the fibers into the direction of force. In addition, cross linking between the collagen fibrils increases the tendon tensile strength. During the repair phase, the mechanically stronger Type I collagen is produced in preference to Type III collagen, thus slightly altering the initial ratio of these fibers to increase the strength of the repair.

Despite intensive remodeling over the following months, complete regeneration of the tendon is never achieved. The tissue replacing the defect remains hypercellular. The diameter of the collagen fibrils is altered, favoring thinner fibrils with reduction in the biomechanical strength of the tendon.

In tendinopathic and ruptured tendons, there is a reduction in the proportion of Type I collagen, and a significant increase in the amount of Type III collagen [30], responsible for the reduced tensile strength of the new tissue due to a reduced number of crosslinks compared to Type I collagen [31]. Recurring microinjuries lead to the development of hypertrophied biologically inferior tissue replacing the intact tendon.

Cytokines and Modulation of Tendon Healing

Growth factors and other cytokines play a key role in the embryonic differentiation of tissue and in the healing of tissues [32]. Growth factors stimulate cell proliferation and chemotaxis and aid angiogenesis, influencing cell differentiation. They regulate cellular synthetic and secretory activity of components of extracellular matrix. Finally, growth factors influence the process of healing.

In the normal flexor tendon of the dog, the levels of basic fibroblast growth factor (bFGF) are higher than the levels of platelet derived growth factor (PDGF). In injured tendons, the converse is true [33]. Under the influence of PDGF, chemotaxis and the rate of proliferation of fibroblasts and collagen synthesis are increased [34]. Fibroblasts of the patellar tendon show increased proliferation in vitro after the administration of bFGF [35]. In addition, an angiogenic effect is evident [36]. During the embryogenesis of tendon, bone morphogenic proteins (BMP), especially BMP 12 and 13, cause increased expression of elastin and collagen Type I. Also, BMP 12 exerts a positive effect on tendon healing [37].

The growth factors of the transforming growth factor beta superfamily induce an increase in mRNA expression of Type I collagen and fibronectin in cell culture experiments [38]. High expression of Type I collagen seems essential to achieve faster healing of tendons. Conse-

quently, there should be a shift from the initial production of collagen Type III to Type I early in the healing process. The aforementioned growth factors could potentially be used to influence the processes of regeneration of tendons therapeutically. However, it is unlikely that a single growth factor will give a positive result. The interaction of many factors present in the right concentration at the right time will be necessary.

Operative Management of Tendinopathy

Each tendon has peculiarities in terms of clinical presentation, specific aspects of conservative and surgical management, recovery etc. The discussion that follows will focus on the Achilles tendon, as it is the most studied and commonly encountered in clinical practice. Also, many of the technical and biological considerations applied to the Achilles tendon can be extrapolated to other tendons.

The natural history of Achilles tendinopathy is still unclear: 24%–45.5% of the patients with Achilles tendinopathy fail to respond to conservative management and will undergo surgery [39,40]. In an 8-year longitudinal study of conservative management of Achilles tendinopathy patients, 24 of the 83 patients (29%) were operated. Seventy patients (84%) had full recovery of their activity level. At 8 years, 78 patients (94%) were asymptomatic or had only mild pain with strenuous exercise. However, 34 patients (41%) started to suffer from Achilles tendinopathy in the initially uninvolved contralateral tendon [24,25].

Surgery is recommended after exhausting conservative methods of management, often tried for at least 6 months. However, long-standing Achilles tendinopathy is associated with poor postoperative results, with a greater rate of re-operation before reaching an acceptable outcome [26]. In general, surgical procedures can be broadly grouped in 4 categories, namely open tenotomy with removal of abnormal tissue without stripping the paratenon; open tenotomy with removal of abnormal tissue and stripping of the paratenon; open tenotomy with longitudinal tenotomy and removal of abnormal tissue with or without paratenon stripping; and percutaneous longitudinal tenotomy [41–47]. The technical objective of surgery is to excise fibrotic adhesions, remove degenerated nodules and make multiple longitudinal incisions in the tendon to detect and excise intratendinous lesions. The biological objective of surgery is to restore vascularity and possibly stimulate the remaining viable cells to initiate cell matrix response and healing [41,43,48–50]. The reasons why multiple longitudinal tenotomies work are still unclear. Recent investigations show that procedure triggers neoangiogenesis in the tendon, with increased blood flow [51]. This would result in improved nutrition and a more favorable environment for healing.

At surgery, the crural fascia is released on both sides of the tendon. Adhesions around the tendon are then trimmed, the hypertrophied paratenon is excised [39]. In addition, longitudinal splits are made in the tendon to identify the abnormal tendon tissues and excise the areas of degeneration. Reconstruction procedures may be required if large lesions are excised [52].

Open Operative Technique

We perform the operation on an outpatient day case basis. The patient is examined immediately pre-operatively to correctly identify and mark the area of maximum tenderness and swelling. We normally do not use a tourniquet but lift the end of the operating table 15 to 20 degrees [53]. The patient lies with the ankles resting on a sandbag or a pillow and the feet dependant over the end of the operating table. A longitudinal slightly curved incision is centered over the abnormal part of the tendon and placed medially, with the concave part toward the tendon. If a lateral approach is used, one should avoid the sural nerve and the short saphenous vein [54,55].

The paratenon and crural fascia are incised and dissected from the underlying tendon. If necessary, the tendon is freed from adhesions on the posterior, medial and lateral aspects. The paratenon should be excised obliquely, as transverse excision may produce a constriction ring that may require further surgery [56]. The fatty tissue anterior to the tendon should be left intact, as the mesotenon contained within it is an important source of vascular supply to the tendon. Areas of thickened, fibrotic and inflamed paratenon are excised. Inspection for areas lacking normal luster and careful palpation for thickening, softening or defects will reveal local sections corresponding to areas of tendinosis within the tendon. These zones can be explored with longitudinal tenotomies. The pathology is identified by the change in texture and color of the tendon. The lesions are then excised, and the defect can either be sutured in a side-to-side fashion or left open: we normally leave it open. Occasionally, if extensive debridement is required, and a major defect in the tendon (>50%) is produced, a tendon transfer may be required [57]. In most cases, the lesions will be well localized, with normal tendon in between.

If used, the tourniquet can be deflated, and hemostasis achieved by diathermy. A below knee lightweight cast is applied with the foot plantigrade, and postoperative immobilization is continued for 2 weeks. Patients are encouraged to bear weight as soon as possible. Greater protection is recommended in patients needing tendon reconstruction. At 2 weeks, the cast is removed and stretching exercises are started. Sport specific training

is started at 3 months and competition is resumed at 6 months.

Complications of Open Surgery

It is remarkable how, for a condition which is relatively common, most studies did not report their assessment procedure, which makes it difficult to compare the results [58,59]. Most authors report excellent or good result in up to 85% of cases, and most articles reporting surgical success rates have over 70% of successful results [58,59]. Schepsis and Leach report good results in patients with paratendinitis and mucoid degeneration [45]. Kvist [13] reports good and excellent results of both paratendinitis and tendinosis. However, this is not always observed in clinical practice [26]. In a recent systematic review of the published postoperative results of surgery for Achilles tendinopathy, we found an inverse relationship between reported success rates and the quality of the scientific methodology used in the study [58,59]. The most common complication following operative management of Achilles tendinopathy is skin breakdown, but deep vein thrombosis and lesions to the sural nerve have been reported.

Outcome of Open Surgery

In the most comprehensive study to date, 432 consecutive patients were followed up longitudinally for 5 months after the surgery. If a complication arose, the patient was followed up clinically for at least 1 year. There were 46 (11%) complications in the 432 patients, and 14 patients with a complication had a re-operation. However, the majority of patients with a complication healed and returned to their pre-injury levels of activity [24].

The long-term effects of operative management are still not fully clarified. The relative underuse of the affected lower limb following surgery results in prolonged calcaneal bone loss despite early weightbearing loading in patients surgically treated for chronic tendinopathy of the main body of the Achilles tendon. The bone loss had not recovered 1 year postoperatively, but in a comparison group there were no significant side-to-side differences 39.5 months postoperatively [60]. Also, calf muscle strength deficit seen on the injured side preoperatively in this group of patients remains despite pain-free and active in sports or at recreational level 5 years after the operation. However, the percentage side-to-side difference is relatively low, and might not have any clinical relevance [61].

Peroneus Brevis Tendon Transfer

We use tendon transfer procedures when the tendinopathic process has required debulking of at least 50% of the main body of the Achilles tendon. We normally use the tendon of peroneus brevis for such procedure [62]. Other authors have used flexor hallucis longus [63].

Operative Technique of Peroneus Tendon Transfer

A 10- to 12-cm longitudinal skin incision is made just medial to the medial border of the Achilles tendon and sharp dissection is carried out through the subcutaneous fat layer. A longitudinal slightly curved incision is centered over the abnormal part of the tendon and placed medially, with the concave part toward the tendon (see above).

The paratenon and crural fascia are incised and dissected from the underlying tendon. If necessary, the tendon is freed from adhesions on the posterior, medial and lateral aspects. The paratenon should be excised obliquely, as transverse excision may produce a constriction ring that may require further surgery [56]. The fatty tissue anterior to the tendon should be left intact, as the mesotenon contained within it is an important source of vascular supply to the tendon. Through longitudinal tenotomies, the pathology is identified. The lesions are then excised, and if the debridement involved 50% or more of the main body of the Achilles tendon, we proceed to perform a peroneus brevis tendon transfer. Through the base of the wound, the deep fascia overlying the deep flexor compartment and the compartment containing the peronei muscles can be seen. The internervous plane lies between peroneus brevis (supplied by the superficial peroneal nerve) and the flexor hallucis longus (supplied by the tibial nerve). The peroneus brevis tendon can be identified towards the medial side. The muscle belly of peroneus brevis passes from the midline medially and under the tendon of peroneus longus to lie anterior to it and adjacent to the posterior aspect of the lateral malleolus. The tendons of peroneus longus and brevis can be distinguished from each other at this level by the fact that, although both tendinous in the distal third of the lower leg, peroneus brevis is muscular more distally than peroneus longus. The deep fascia overlying the peroneal tendons is incised and the peroneal tendons are mobilized.

Peroneus brevis passes around the posterior aspect of the lateral malleolus and above the peroneal trochlea to insert onto the styloid process of the base of the fifth metatarsal. The peroneal tendons are bound down both at the level of the lateral malleolus and at the level of the peroneal trochlea by the superior peroneal retinaculum and the inferior peroneal retinaculum, respectively. A 2.5-cm longitudinal incision is made over the base of the fifth metatarsal. The peroneus brevis tendon is identified, a stay suture is placed in the distal end of the peroneus brevis tendon, the tendon is detached from its insertion and mobilized proximally. The tendon is then delivered through the posteromedial wound using gentle continu-

ous traction as it is pulled through the inferior peroneal retinaculum. In this fashion, the tendon of peroneus brevis retains its blood supply from the intermuscular septum.

The peroneus brevis tendon is then weaved through the Achilles tendon starting from lateral to medial in a distal to proximal direction via coronal incisions medially and laterally in the Achilles tendon. The edges of the coronal incisions in the Achilles tendon are sutured to the peroneus brevis tendon to prevent progression of the incision that would lead to the peroneal tendon cutting out. The tendon is then passed through the Achilles tendon with the foot in physiological plantar flexion to maintain the correct tension. At times, the tendon of plantaris can be harvested to reinforce the reconstruction.

Postoperative Management

The limb is elevated on a Braun frame and, following review by a physiotherapist, the patient is generally discharged the day following surgery. A full below knee cast is applied with the ankle in natural equinus and retained for 2 weeks until outpatient review. Patients are allowed to bear weight on tip toes of the operated leg as tolerated, but are told to keep the leg elevated as much as possible until seen in the clinic, when the cast is removed. The lower limb is left free, and patients are encouraged to bear weight on the operated limb as soon as they felt comfortable, and to gradually progress to full weight-bearing. The patients are taught to perform gentle mobilization exercises of the ankle, isometric contraction of the gastroc-soleus complex, and gentle concentric contraction of the calf muscles. Patients are encouraged to perform mobilization of the involved ankle several times per day. Patients are given an appointment 6 weeks from the operation, when they are referred for more intensive physiotherapy. They are allowed to begin gentle exercise such as swimming and cycling at 8 weeks following surgery.

Experimental Operative Procedures

Percutaneous Longitudinal Tenotomy

In patients with isolated Achilles tendinopathy with no paratendinous involvement and a well defined nodular lesion less that 2.5 cm long, we have used multiple percutaneous longitudinal tenotomies when conservative management has failed. An ultrasound (US) scan is used to confirm the precise location of the area of tendinopathy. Patient are mobilized as soon as able [46,47,55]. If the multiple percutaneous tenotomies are performed in the absence of chronic paratendinopathy, the outcome is comparable to that of open procedures. In addition, the procedure is simple and can be performed under local anesthesia without a tourniquet, but attention to details is necessary, as complications occur even in minimally invasive procedures.

In patients with diffuse or multinodular tendinopathy or with pantendinopathy, a formal surgical exploration with stripping of the paratenon and multiple longitudinal tenotomies may be preferable [47].

Operative Technique for Percutaneous Longitudinal Tenotomy

Patients are operated as day cases. The patient lies prone on the operating table with the feet protruding beyond the edge, and the ankles resting on a sandbag. A bloodless field is not necessary. The tendon is accurately palpated, and the area of maximum swelling and/or tenderness marked, and checked again by US scanning. The skin and the subcutaneous tissues over the Achilles tendon are infiltrated with 10 to 15 mL of plain 1% lignocaine (Lignocaine Hydrochloride, Evans Medical Ltd, Leatherhead, England).

A number 11 surgical scalpel blade is inserted parallel to the long axis of the tendon fibers in the marked area(s) with the cutting edge pointing cranially. Keeping the blade still, a full passive ankle dorsi-flexion movement is produced. After reversing the position of the blade, a full passive ankle plantar-flexion movement is produced. A variable, but probably in the region of 2.8 cm long, area of tenolysis is thus obtained through a stab wound. The procedure is repeated 2 cm medial and proximally, medial and distally, lateral and proximally and lateral and distally to the site of the first stab wound. The 5 wounds are closed with Steri-Strips, dressed with cotton swabs, and a few layers of cotton wool and a crepe bandage are applied.

Operative Technique of Ultrasound-Guided Percutaneous Longitudinal Tenotomy

Patients are operated as outpatients. The patient lies prone on the examination couch with the feet protruding beyond the edge, and the ankles resting on a sandbag. A bloodless field is not necessary. The tendon is accurately palpated, and the area of maximum swelling and/or tenderness marked, and checked by US scanning. The skin is prepped with an antiseptic solution, and a sterile longitudinal 7.5 MHz probe is used to image again the area of tendinopathy. Before infiltrating the skin and the subcutaneous tissues over the Achilles tendon with 10 ml of 1% lignocaine (Lignocaine Hydrochloride, Evans Medical Ltd, Leatherhead, England), 7 ml of 0.5% lignocaine (Lignocaine Hydrochloride, Evans Medical Ltd, Leatherhead, England) are used to infiltrate the space

between the tendon and the paratenon, to try and distend the paratenon and break the adherences that may be present between the tendon and the paratenon.

Under US control, a number 11 surgical scalpel blade (Swann-Morton, England) is inserted parallel to the long axis of the tendon fibers in the centre of the area of tendinopathy, as assessed by high resolution US imaging. The cutting edge of the blade points caudally, and penetrates the whole thickness of the tendon. Keeping the blade still, a full passive ankle plantar-flexion is produced. The scalpel blade is then retracted to the surface of the tendon, and inclined 45 degrees on the sagittal axis, and the blade is inserted medially through the original tenotomy. Keeping the blade still, a full passive ankle plantar-flexion is produced. The whole procedure is repeated inclining the blade 45° laterally to the original tenotomy, inserting it laterally through the original tenotomy. Keeping the blade still, a full passive ankle plantar-flexion is produced. The blade is then partially retracted to the posterior surface of the Achilles tendon, reversed 180 degrees, so that its cutting edge now points caudally, and the whole procedure repeated, dorsiflexing the ankle passively. Preliminary cadaveric studies showed that a tenotomy 2.8 cm long on average is thus obtained through a stab wound in the main body of the tendon [55]. A Steri-Strip (3M United Kingdom PLC, Bracknell, Berkshire, England) can be applied on the stab wound, or the stab wound can be left open [64]. The wound is dressed with cotton swabs, and a few layers of cotton wool and a crepe bandage are applied.

Postoperative Management

On admission, patients are taught to perform isometric contractions of their triceps surae [65]. Patients are instructed to perform the isometric strength training at 3 different angles, namely at maximum dorsi-flexion, maximum plantar flexion and at a point midway between the two.

The foot is kept elevated on the first postoperative day, and oral analgesia is administered as requested for pain control. Early active dorsi- and plantar flexion of the ankle are encouraged [66]. Patient are allowed to walk using elbow crutches weight-bearing as able. Full weight-bearing is encouraged after the second postoperative day, when the bandage is reduced to a simple adhesive plaster over the wounds and an elasticated compressive sock, to be removed at night. Stationary bicycling, and isometric, concentric and eccentric strengthening of the calf muscles is started at that stage under physiotherapist guidance.

Gentle jogging on an elastic trampoline is permitted after 2 weeks, when the sock and the adhesive plaster are removed. Swimming and water running are encouraged from the second week. Gentle running is started 4 to 6 weeks after the procedure, and mileage gradually increased. Hill workouts or interval-training are allowed after a further 6 weeks, when return to normal training is allowed.

Ultrasound-guided percutaneous longitudinal tenotomy is simple, requires only local anesthesia, is performed without a tourniquet, and allowed the return to high sporting levels of the majority of the athletes with a tendinopathy of the main body of the tendon. Early postoperative mobilization probably prevents the formation of adhesions, and a single skin wound most likely limits morbidity. In most instances, the affected tendon remained thicker than the healthy one, and the clinical results are comparable with those reported using more extensive procedures [15,16].

Arthroscopic Procedures

Arthroscopy is now in the armamentarium of orthopedic surgeon for the routine management of rotator cuff disorders [67].

"Tendoscopy" has been used by several authors to approach in a minimally invasive fashion a variety of tendinopathic tendons, including tibialis anterior [68], Achilles tendon, where the surgical endoscopic technique includes peritenon release and debridement, and longitudinal tenotomies [69,70]; patellar tendon [71]; peroneal tendons [72]; tibialis posterior [73]; tennis elbow [74] with encouraging results. Some authors have used arthroscopic techniques for biceps tenodeses [75]. Given the limited field of vision that there techniques involve, care must be taken to avoid iatrogenic lesion of the surrounding tissues.

To our knowledge, only one study has compared arthroscopic techniques with classical open techniques [76]. In that study, which focussed on the patellar tendon, arthroscopic patellar tenotomy was as successful as the traditional open procedure, and both procedures provided virtually all subjects with symptomatic benefit. However, only about half the subjects who underwent either open or arthroscopic patellar tenotomy were able to compete at their former sporting level at follow-up.

Muscle Transfer to the Body of the Tendon

Longitudinal tenotomies increase the blood supply of the degenerated area [51]. Recently, in a rabbit model, following longitudinal tenotomy we have performed a soleus pedicle graft within the operated tendon, and shown that the transplanted muscle was viable and had integrated well within the tendon tissue 3 months after

the transplant, without transforming into connective tissue. Hypervascularization of the graft tissue, probably due to the operation, was also observed, together with neoangiogenesis up to 3 months after the operation [77].

A Difficult Problem: Calcific Insertional Tendinopathy

Some patients may present with tendinopathy at the insertion of the Achilles tendon on the calcaneus [78]. Occasionally, a digitation of bone from the calcaneus to the Achilles tendon is radiographically evident, and is associated with retrocalcaneal bursitis [79]. In these patients, following failure of conservative management [18,80], surgery includes bursectomy, excision of the diseased tendon, and resection of the calcific deposit [81,82].

Patients undergo surgery as day cases. With the patient prone under general anesthesia with a thigh tourniquet inflated to 250 mmHg to provide hemostasis after the limb had been exsanguinated, the Achilles tendon is exposed through a longitudinal incision 1 cm medial to the medial border of the tendon. The incision is extended from the lower one-third of the tendon to up to 2 cm distal to its calcaneal insertion. At times, it is necessary to curve the incision transversely and laterally in a hockey stick fashion. Sharp dissection is continued to the paratenon, which is dissected from the tendon and excised, taking care to preserve the anterior fat in Kager's triangle and not to injure the mesotenon. The retrocalcaneal bursa is excised. The tendon is inspected for areas which have lost their normal shining appearance, and palpated for areas of softening or thickening. The areas which have lost their normal shining appearance, and the areas which are softer or thicker areas are explored via 1 to 3 longitudinal tenotomies, and areas of degeneration are excised. The longitudinal tenotomies are not repaired [8]. The area of calcific tendinopathy is identified, and its proximal, medial and lateral edges defined using the tip of a syringe needle. The calcific area is then exposed starting from its proximal and medial aspect. If necessary, the Achilles tendon surrounding the area of calcific tendinopathy is detached by sharp dissection. The area of calcific tendinopathy is excised from the calcaneus. The area of hyaline cartilage at the postero-superior corner of the calcaneus is excised using an osteotome, and, if needed, its base paired off with bone nibblers. The tendon is re-inserted in the calcaneus using 2 to 5 bone anchors [Mitek GII, Ethicon Ltd., Edinburgh, Scotland). Three bone anchors are used if 50% to 75% of the Achilles tendon had been dis-inserted. Four bone anchors are used if 75% or more of the Achilles tendon had been dis-inserted, and 5 bone anchors are used if the Achilles tendon has been totally dis-inserted. The Achilles tendon is advanced in a proximal to distal fashion, and reinserted in the calcaneum. A tendon augmentation or a tendon transfer is rarely necessary.

After release of the tourniquet, hemostasis is achieved by diathermy. The wound was closed in layers using absorbable sutures.

Postoperative Management

The skin wound is dressed with gauze, and sterile plaster wool applied. A synthetic below knee cast with the ankle plantigrade is applied. Patients are discharged the day of surgery within 8 hours of the operation. Patients are asked to mobilize with crutches under the guidance of a physiotherapist in the immediate postoperative period. Patients are allowed to bear weight on the operated leg as tolerated, but were told to keep the leg elevated as much as possible for the first 2 postoperative weeks. The cast is removed 2 weeks after the operation. A synthetic anterior below knee slab is applied, with the ankle in neutral. The synthetic slab is secured to the leg with 3 or 4 removable Velcro (Velcro USA Inc., Manchester, NH, USA) straps for 4 weeks. The patients are encouraged to continue to bear weight on the operated limb, and to gradually progress to full weightbearing, if they are not already doing so. The patients are taught gentle mobilization exercises of the ankle, isometric contraction of the gastroc-soleus complex, and gentle concentric contraction of the calf muscles. Patients are encouraged to perform mobilization of the involved ankle several times per day after unstrapping of the relevant Velcro strap(s). The anterior slab is removed 6 weeks from the operation.

Stationary cycling and swimming was recommended from the second week after removal of the cast. We allow return to gentle training 6 weeks after removal of the cast. Gradual progression to full sports activity at 20 to 24 weeks from the operation is planned according to the patients' progress. Resumption of competition depends on the patients' plans, but we do not recommended before 6 months after surgery.

Methods of Evaluation

Several quantitative tests of ankle function [83] have been used to measure outcome in Achilles tendinopathy. However, condition-specific numerical scales generally have greater sensitivity and specificity than do general-purpose scales [84]. A specific scale for patients with patellar tendinopathy [83] has recently been published, and we have recently devised a self-administered ques-

tionnaire-based instrument to measure the severity of Achilles tendinopathy, the VISA-A [84]. There is a need for a quantitative index of pain and function in patients with Achilles tendinopathy. The VISA-A questionnaire appears a valid, reliable and easy-to-administer measure of the severity of Achilles tendinopathy, and seems suitable for both clinical rating and quantitative research.

Conclusions

Surgery for chronic overuse tendon conditions, even when successful, does not reconstitute a normal tendon. Mostly, the result is functionally satisfactory despite morphological differences and biomechanical weakness compared to a normal tendon. The therapeutic use of growth factors by gene transfer, it seems, may produce a tendon which is biologically, biomechanically, biochemically, and physiologically more "normal."

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Part IV
New Developments

26
Research Methodology and Animal Modeling in Tendinopathy

Joanne M. Archambault and Albert J. Banes

Tendon injuries arising from overuse are a difficult clinical problem. Lack of information about their etiology makes the pursuit of effective treatments almost a random process. Some components of the mechanical environment seem to contribute to the manifestation of tendinopathies. To devise proper treatments, we must first understand how loading affects tendons at the cellular and molecular levels. This chapter will review some of the current basic science methods used to understand tendon biology and mechanics, both in injury and non-injury situations. The first 2 parts will focus on studies done to understand tendinopathies in animal models (*in vivo*), while the third and fourth parts will describe some of the research methodologies (*ex vivo* and *in vitro*) that have been used to understand the mechanisms that control a tendon's response to mechanical loads.

Animal Models of Tendinopathies Induced by Overuse

This section describes animal models in which tendons have been subjected to repeated mechanical loads, usually via muscle stimulation. In some cases, these loading protocols resulted in an injury reaction, but in other cases they did not.

One of the first models of acute overuse injury to a tendon was presented by Rais [1]. An inflammation of the Achilles paratenon with crepitation was induced in the Achilles tendon of young rabbits. With a kicking machine, 150 flexion/extension movements of the ankle were done per minute with simultaneous muscle contraction of the plantar flexors. Edema and an inflammatory cell infiltrate were present after 6 hours of exercise. The changes were dependent on the duration of exposure. Two weeks after the single loading session, there was new collagen formation, along with hypercellularity and hypervascularity in the paratenon.

Backman and coworkers [2] used a similar protocol to the one used by Rais [1], but in a chronic manner. Loading sessions of 2 hours in duration were done 3 times per week, for 5.5 weeks. All animals had irregular thickening over their Achilles tendon and palpable nodules. In the paratenon, there was an increased number of fibroblasts and capillaries, as well as edema and an infiltration of inflammatory cells, mostly lymphocytes. Backman and coworkers [2] also described degenerative processes that included changes in the staining affinity of the tendon, fibrils of varying thickness, and nuclei of varying size. Although the inflammatory changes in the paratenon were consistent, degenerative changes in the tendon were of varying severity. In a related study, it was also reported that blood flow to the tendon and paratenon of the experimental leg was twice that of the contralateral leg after the 5.5 weeks of loading [3].

Archambault and coworkers [4] reproduced this rabbit model but used skeletally mature animals, a longer protocol and a lower movement frequency (75 contractions per minute vs. 150 contractions per minute used by Backman and Rais in their respective studies). After 11 weeks of loading the rabbit Achilles tendon, no changes were observed in the paratenon or the tendon that were suggestive of an injury response. One major difference in the models is that Archambault and coworkers [4] used a lower movement frequency. It has been suggested that rapid movement of a tendon in its sheath may result in injury [5]. A higher movement frequency results in more gliding events between the sheath (or paratenon) and the tendon, possibly increasing the likelihood of injury.

Smutz and coworkers [6] evaluated a low-force, high-frequency protocol on the wrist tendons of adult rhesus monkeys. For 6 hours per day, 5 days per week, and for 3 weeks, the wrist flexor and extensor muscles were electrically stimulated. This repetitive motion protocol had no detectable effect on the wrist tendons, and no signs of pathology or inflammation were noted in the carpal tunnel. This report and the one by Archambault and

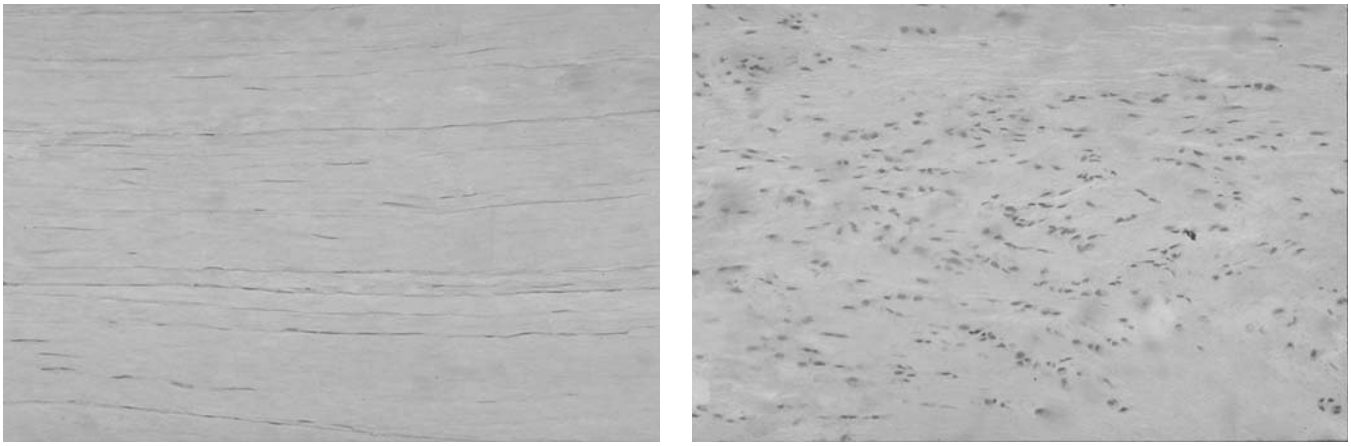

Figure 26-1. Histological section of representative control rat supraspinatus tendon (left photo) and tendon from a rat with 8 weeks of downhill treadmill running (right photo). Tendons from the overuse running group had increases in cellularity and collagen disorganization when compared to tendons from control animals. (From [7], with permission.)

coworkers [4] suggest that tendons are not easily injured in adult animals using a controlled loading protocol. Note that tendon injuries were induced in immature animals in the studies of Backman and Rais.

Recently, Soslowsky and coworkers [7] were successful in inducing degenerative changes in the rat supraspinatus tendon. Rats were trained to run downhill on a treadmill for 1 hour per day, 5 days per week, for 4, 8, or 16 weeks. The experimental tendons had a statistically lower maximum load to failure, and a lower maximum stress capacity than tendons from unexercised (control) animals, but had a greater cross-sectional area. There was increased cellularity, collagen disorganization, and changes in cell shape in the experimental tendons when compared with the control tendons (Figure 26-1). This model of tendinopathy in the rat shoulder most closely approximates a reproducible tendinopathy. With this model, it may be possible to probe how the tendon cells respond to overuse, infer causative mechanisms and derive scientifically-based therapeutic interventions.

There have been 2 reports of the induction of overuse tendinopathy in chickens [8] and of partial failure at the bone-tendon junction of the humeral epicondyle of rabbits induced by muscle stimulation [9]. However, details of these models are lacking.

Tendinopathies have been reported to occur spontaneously in dogs [10] and horses [11,12]. Very good work has been done in the veterinary field on the diagnosis and histopathology of injuries to the equine superficial digital flexor tendon (SDFT). Ultrasound imaging, thermography and ground reaction force patterns have been correlated to injury development, often in a prospective manner [13–15]. In addition, a good relationship between ultrasonographic findings and histological changes in injured horse tendons was demonstrated by Marr and coworkers [16]. Ultrasound technology allows for the monitoring of tendon changes during an overuse protocol without sacrificing the animal at a time point earlier than necessary to demonstrate changes.

In this same paper [16], the only real staging of tendinopathies that is currently available has been described. Injuries of less than 2 weeks duration showed hemorrhage, edema, fibrolysis, fibrin deposition, and inflammatory tissue. Injuries of one to 5 months duration showed fibroplasia and granulation tissue. Injuries of over a one-year duration showed various degrees of fibrosis, increased number of cells, irregular arrangement of collagen, widespread scar formation and hemosiderin deposition. Fibrosis of the paratenon was also common at this stage. Marr and coworkers [16] suggested a mechanical etiology to the observed pathology: the initial disruption of the tendon induces dissolution of the tendon matrix and fiber lysis caused by the release of collagenases and proteases from damaged cells and from inflammatory cells attracted to the site of injury. What follows is a typical wound healing response, with new matrix deposition and remodeling. Inflammation was observed in the very early stages of the pathology, but not at the later stages.

There has been ongoing controversy about the role of inflammation in overuse tendinopathies [17]. In tendon specimens from end-stage tendinopathy, few signs of classical inflammation have been observed [18,19]. This has led researchers to conclude that inflammation is not part of tendon degeneration. This is an erroneous conclusion since these observations only indicate that there is no inflammation with cellular infiltrates at the end-stage of pathology. Moreover, since tendinopathies have not been staged, the pathology may have been initiated months or years prior to detection. There may have been inflamma-

tion at some point in the initial stages of tendon degeneration, which would have resolved by the time a tendon rupture occurred or the tendon was biopsied during surgery. Cytokine induction of matrix metalloproteinases and other proteases might be a mechanism by which matrix degeneration occurs.

Animal Models of Tendinopathies Induced by Chemical Means

Collagenase has been injected into tendons in an effort to model the pathological changes observed in human tissues. The validity of this approach has been questioned because it does not directly simulate the overuse process. In addition, other models have been developed to study rheumatoid tenosynovitis [20] and antibiotic-induced tendinopathy.

Williams and coworkers [21,22] injected collagenase into the superficial digital flexor tendon of horses to induce tendinopathy and investigated the sequence of events associated with the healing of this injury. The severity of the pathology was related to the amount of collagenase injected. After a transient inflammatory response, a classical wound healing process occurred with formation of granulation tissue and increased staining for Type III collagen and fibronectin. Reorganization of the matrix continued until 14 months, the last time point studied, but normal structure had not been reestablished. The authors pointed out that the morphological characteristics and time course of repair following the collagenase injection were similar to those of a natural, exercise-induced trauma.

Collagenase has also been injected into the supraspinatus tendon of the rat [23]. This procedure produced a marked disruption of the collagen matrix and fibroplasia. At 12 weeks following the injection, these changes were still present, but to a lesser extent than the earlier time points, suggestive of a resolution process. Stone and coworkers [24] injected collagenase into the patellar tendon of rabbits, and compared it to the injection of a cytokine cocktail. The exact composition of the cytokine preparation was not described in their publication, but it included Interleukin-1α, Transforming Growth Factor-β, basic Fibroblast Growth Factor and other cytokines that would have been produced by rabbit synovial fibroblasts exposed to phorbol 12-myristate acetate, a strong tumour promoting agent, in culture. At 16 weeks post-collagenase injection, small myxoid foci were detected with disorganized collagen. The cytokine injection did not cause the collagen matrix disorganization observed in the collagenase-injected tendons, however there was an increase in cellularity. Since the cytokine preparation included agents that could both stimulate (i.e. IL-1α) and inhibit collagenase expression (i.e. TGFβ) in fibroblasts, the experimental effect were weaker than the effects associated with the collagenase-only injections (Figure 26-2).

Collagenase injections produce tendinopathy that is remarkably similar to the histologic appearance of end-

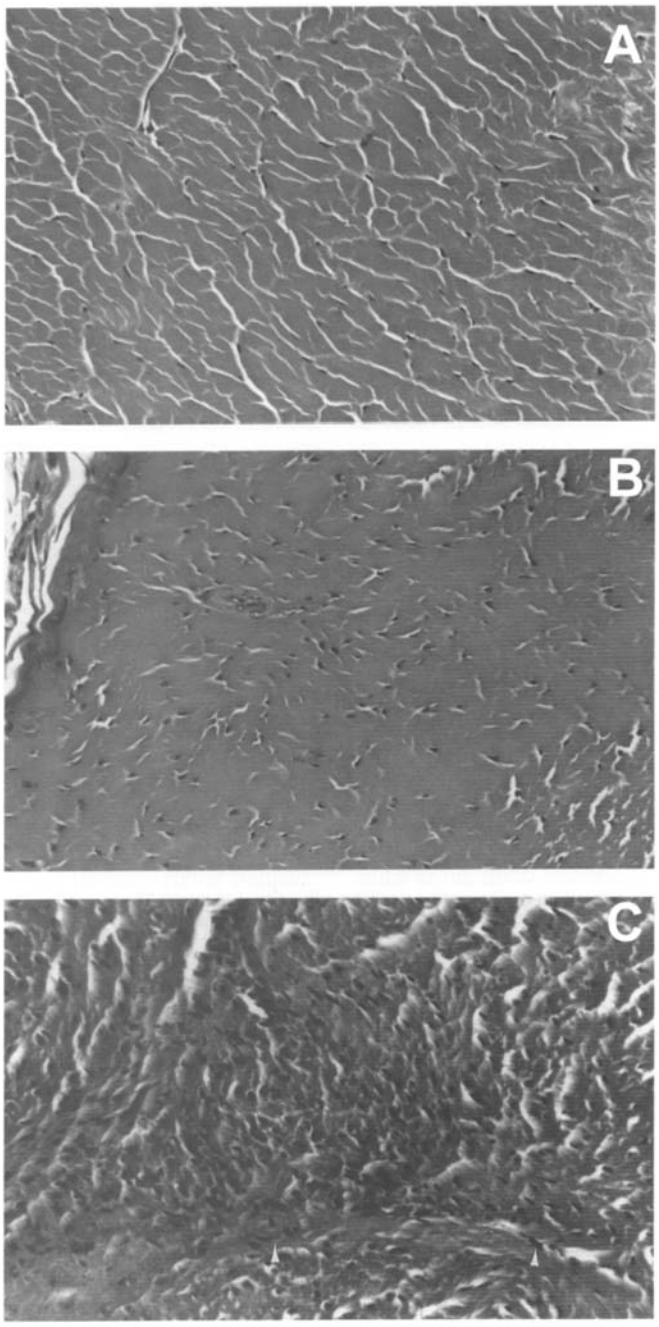

FIGURE 26-2. Histological section of rabbit patellar tendon 4 weeks after injection of saline (A), cytokine preparation (B) or collagenase (C). The cytokine-injected tendons demonstrated a slight increase in cellularity, while collagenases-injected tendons were hypercellular, hypervascular and had disorganized matrix. (From [24], with permission.)

stage pathological specimens in humans. However, there is no evidence that collagenase is involved in human tendinopathies. Collagenase might be released into the tendon during the inflammation that some have suggested accompanies microtrauma [25] or tendon cells may produce collagenase in response to excessive loading. Preliminary results suggest that the rabbit Achilles tendon does not produce collagenase in response to one bout of overuse of up to 6 hours duration, but does produce collagenase when placed in organ culture [26]. If active collagenase was found in surgical specimens or ruptured tendons, this would give credence to the collagenase injection approach. However, evidence that collagenase is produced over time in an animal model of tendon overuse would be stronger support for its role in tendinopathies.

Achilles tendinopathy and ruptures have been associated with fluoroquinolone antibiotics [27]. Ruptured tendons had irregular collagen fiber arrangement, hypercellularity, and increased glycosaminoglycan staining—pathological features that are very similar to the degenerative changes described previously in athletic tendinopathies [28]. The mechanisms involved in this induction of tendinopathy are not known, however this class of antibiotics appears to have a toxic effect on tendon cells [29]. After 3 days of oral antibiotic administration to rats, cells in the Achilles tendon showed degenerative alterations, and there was a loss of cell-matrix interactions. These results are mentioned to provide an appreciation of the powerful effects that biochemical agents can have on tendons—tendon ruptures occured within 2 weeks of the start of antibiotic treatment in 50% of the cases [30]. Tendon degeneration in antibiotics-related cases occurs much more quickly than in overuse-related cases, indicating that healthy tendon cells are the key to maintaining normal tendon structure. It would be short-sighted to think that tendinopathies are only a function of overuse and loading. If this were the case, every person who engages in sports or work that involves repetitive movement might sustain a tendinopathy. However, as this does not occur, there might be a genetic predisposition to these injuries.

Research Methodology (*ex vivo* Systems)

Although investigations with *in vivo* animal models might be the best way to simulate and stage the tendinopathy process that occurs in humans, the *in vivo* situation is very complex. The animal's age, gender, physiology, genetics, behavior, nutrition, etc. may all have an effect on the outcome, or be confounding variables in the process. Research done with tendons in culture allows for a single experimental variable to be manipulated. For example, *ex vivo* experiments can be used to study the effects of repetitive loading on tendons, without the systematic biochemical and hormonal responses to exercise that occur simultaneously in the animal.

Slack and coworkers [31] first showed that tendons could be maintained in organ culture. Using embryonic chick tendons, they showed that protein and DNA synthesis increased in tendons that were experimentally loaded in culture for 48 to 72 hours, versus tendons that were cultured on steel grids. Hannafin and coworkers [32] reported that cyclic tension in culture for 2 hours per day could maintain the mechanical properties of the tendon. If tendons were cultured without tension, the tensile modulus decreased to 68% of control tendon (noncultured) in a 4-week period. This is an important finding for *ex vivo* research methodologies, since it indicates that tension is necessary for the tendon properties to remain as close as possible to those of the *in vivo* system, where the tendon is always under some degree of tension. Also, collagenase is expressed and produced very quickly in tendons in culture when they are not under tension (J. Archambault, S. Arnoczky, unpublished work). This tendon-derived collagenase could be responsible for degrading tendon matrix, and lead to the reduced mechanical properties observed in cultured, unloaded tendons.

Mechanical loading devices are important research tools that allow for multiple tendons to be loaded simultaneously in culture. Such a device has been used at the University of North Carolina to cyclically load tendons in culture and evaluate the corresponding biological responses (Figure 26-3). Banes and coworkers [33] reported that 8 hours of load per day at 0.65% elongation for 3 days stimulated DNA and collagen synthesis in whole avian flexor tendons. The load effect could be blocked by gap junction inhibitors, indicating the importance of intercellular communication in tendons. In addition, cyclically loaded tendons at 0.5 Hz for 5 days at about 20% of the tendon's ultimate tensile stress resulted in significantly greater strain accumulation in the loaded compared to the unloaded tendons [34]. The mechanical stimulus also reduced the number of apoptotic cells observed in the unloaded cultured tendons.

An important application of tendon loading in culture is the evaluation of the biological responses to fatigue loading protocols. As a tendon fatigues, either with static or cyclic loading, there is a significant decline in its mechanical properties [35]. Overuse tendinopathies may have a component of material fatigue, as the tendon is loaded throughout its lifetime. A tendon rupture could be considered the equivalent of a fatigue rupture in an engineering material. The amount of damage done by a

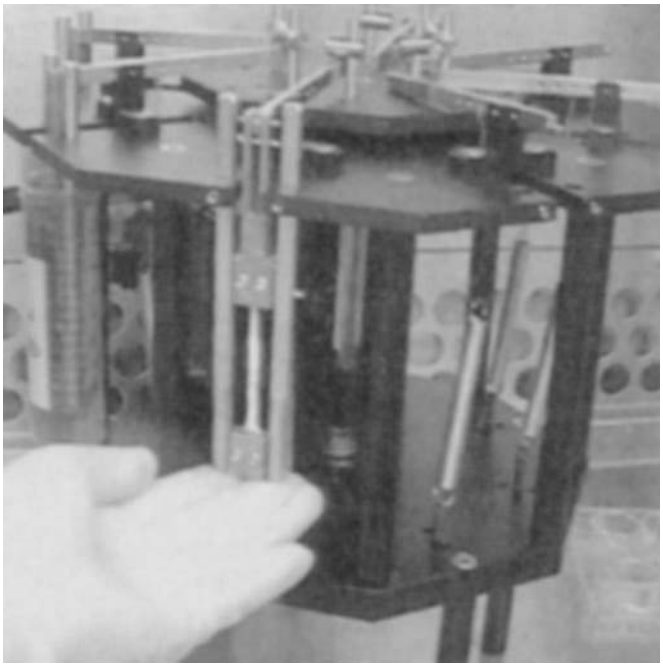

FIGURE 26-3. Photograph of a chicken flexor digitorum profundus tendon clamped into a loading frame of a multi-station tendon loading device. (From [33], with permission.)

loading protocol is a function of the number of loading cycles and the amount of stress. Tendons differ from engineering materials in that they have the ability to repair damage. One of the causes for overuse injuries in tendons may be a breakdown in the balance between fatigue damage and routine repair [36]. If either the damage resulting from the loading regime is excessive or the ability of the cells to repair damage is compromised, the damage may accumulate and result in a tendinopathy. An *ex vivo* tendon loading system could be used to evaluate the biological response of tendons to various amounts of fatigue damage. A threshold of loading may exist above which a tendon cannot fabricate enough matrix to keep pace with the rate of damage, leading to a decline in the tendon's mechanical properties. Such information may be important to understanding if repetitive loading results in a disengagement of anabolic and catabolic states in tendon cells.

Organ cultures have been used recently to evaluate the effect of hypoxia on tendons [37].

Flexor digitorum profundus tendons of rabbits were incubated under various degrees of oxygen tension. Although cell proliferation, synthesis of non-collagenous proteins, and synthesis of proteoglycans were not affected, hypoxia inhibited collagen synthesis. This result suggests that hypoxia may reduce collagen synthesis, or the repair rate of tendons, a potentially deleterious effect if it were combined with damage from cyclic loading.

Research Methodology (*in vitro* Systems)

In vitro experiments allow researchers to apply well-defined mechanical stimulation to isolated tendon cells. Cells can be subjected to fluid-induced shear stress, compression, or stretching. In the latter case, cells attached to a substrate are deformed when the substrate is deformed. These systems are best suited for evaluating the molecular and cellular responses of tendon cells to mechanical stimulation, the mechanisms of transduction of these mechanical signals and the effect of various drugs. They may provide some clues as to which biochemical factors could then be evaluated in more complex systems, such as the *ex vivo* and *in vivo* models described previously.

Banes and coworkers [38] first showed that tenocytes responded to mechanical loading *in vitro* by altering expression of actin and tubulin. Almekinders and coworkers [39] reported that human tenocytes responded to repetitive stretching by producing PGE_2. The production of PGE_2 was greater at higher frequencies and could be blocked by the NSAID indomethacin. Wang and coworkers had similar findings when they stretched human tenocytes residing on a microgrooved surface [40]. They also demonstrated that PGE_2 production depended on the stretching magnitude: with 4% strain, PGE_2 production was similar to non-stretched cells, but, at 8% and 12% strain, PGE_2 was significantly increased. Since PGE_2 is thought to be important in inflammation and pain, general and specific COX inhibitors have been used as a treatment for tendinopathies. It is difficult to justify this type of treatment since PGE_2 has not been found in painful human Achilles tendons [41]. It is also possible that tenocytes release PGE_2 in response to mechanical stimulation as do bone cells [42], and that blocking this release might be detrimental to normal functioning of the tendon.

Stretching of tenocytes has also been shown to induce the expression of novel genes [43], and activate the association of proteins that are part of focal adhesions [44]. Other *in vitro* work with tenocytes has shown that cytokines and growth factors can interact with mechanical stimulation to produce effects that do not occur when the mechanical load is applied alone. Banes and coworkers [45] showed that mechanical load by itself does not stimulate cell division, but that it does when growth factors such as IGF-I and PDGF-BB are present. Archambault and coworkers [46] showed that stretching tenocytes in the presence of IL-1β leads to a greater release of MMP-3 than when either stretching or IL-1β were applied in isolation. Such combination effects may be important to the *in vivo* system: mechanical loading by itself may not cause a cellular response, but an altered

Table 26-1. Summary of animal models of tendinopathy

Reference	Animal	Target tendon	Means	Result
Rais 1961	Rabbit	Achilles	Acute muscle stimulation	Paratenon inflammation
Backman et al. 1990	Rabbit	Achilles	Chronic muscle stimulation	Paratenon inflammation and tendon degeneration
Archambault et al. 2001a	Rabbit	Achilles	Chronic muscle stimulation	No changes
Smutz et al. 1994	Monkey	Wrist flexors	Chronic muscle stimulation	No changes
Soslowsky et al. 2000 Carpenter et al. 1998	Rat	Supraspinatus	Chronic treadmill running	Tendon degeneration and decline of mechanical properties
Lai et al. 1995	Chicken	Gastrocnemius	Ablation overload	Less collagen material
Han et al. 1995	Rabbit	Lateral common extensor	Acute muscle stimulation	Partial failure at lateral epicondyle
Sakata et al. 1988	Rabbit	Tibialis anterior	Antigen injection	Inflammation of synovial sheath
Williams et al. 1984a, 1984b	Horse	Superficial digital flexor	Collagenase injection	Acute inflammation, disruption of matrix, more type III collagen & fibronectin
Soslowsky et al. 1996	Rat	Supraspinatus	Collagenase injection	Disruption of matrix, hypercellularity
Stone et al. 1999	Rabbit	Patellar	Collagenase injection Cytokine injection	Disruption of matrix, hypercellularity
Shakibaei et al. 2001	Rat	Achilles	Oral fluoroquinolone antibiotics	Degenerative alterations, loss of cell-matrix interactions

biochemical environment may be enough to produce a tendon injury. Carpenter and coworkers [47] reported that damage to the supraspinatus tendon in rats was greater when the overuse protocol was combined with an intrinsic (collagenase injection) or extrinsic (external compression on tendon) injury.

Recent data demonstrated that cyclic straining of tenocytes led to an immediate upregulation of a stress-activated protein kinase, pJNK, that is an upstream regulator of apoptosis. This up-regulation was strain but not frequency dependent, with a much stronger up-regulation observed at 6% than 3% strain [48]. pJNK upregulation returned to normal levels after 2 hours of stretching, but persisted if the tendon cells were simultaneously exposed to environmental stresses such as hyperthermia and hyperosmolarity [49]. This is another example of combined stimuli producing a greater cellular response than mechanical loading alone.

Conclusions

Although there is interest in understanding the causes of tendinopathies, research into this topic is still in its infancy. Hopefully this chapter has provided insights into the current knowledge of experimental aspects of tendon overuse injury and damage. Table 26-1 summarizes the important features of the animal models of tendinopathies discussed in this chapter. *In vivo* animal models are the gold standard for understanding tendinopathies, but research done with *ex vivo* and *in vitro* systems have made an important contribution to our understanding.

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27
Tendon Innervation and Neuronal Response After Injury

Paul W. Ackermann, Daniel K-I. Bring, and Per Renström

Introduction

Tendon pain and injuries are frequent complications of repetitive motion and overuse syndromes and pose a huge burden on the health care system mainly due to the lack of specific treatment and long recovery time until return to work. The knowledge of the pathomechanisms underlying tendon disorders is still limited. Although some mechanical risk factors have been identified, the relationship between pain and inflammation is debatable [54], and still requires a plausible biological explanation. Accumulating data support the hypothesis that the peripheral nervous system plays a major role in the regulation of pain and inflammation, maybe also in tissue repair.

In inflammatory conditions of the musculoskeletal system, pain is almost a constant feature. However, in degenerative conditions pain is highly variable. Whether inflammation is a prerequisite to pain in degenerative disease is unclear. Notably, spontaneous ruptures of tendons, presumed to be caused by degeneration, are often not preceded by pain. On the whole, the relationship between pain, inflammation and degeneration of the musculoskeletal system, and specifically tendons, remains obscure, a consequence of our limited knowledge of neuroanatomy and pathophysiology.

Over the last decade, however, knowledge about specific neuronal signal substances involved in the regulation of pain, inflammation and tissue repair has evolved. This chapter discusses tendon innervation focusing on neuronal mediators, so-called neuropeptides, including opioids, in tendon proposing an endogenous peripheral system of pain inhibition. Moreover, recent findings on neuronal response to injury are presented, suggesting new pathways for tendon repair.

The novel data presented in this chapter considering tendon innervation and neuronal response to injury may suggest new targets for pain treatment and specific pharmacotherapy in tendon disorders that could shorten recovery time.

Tendon Innervation

Tendon innervation originates from 3 neighboring sources, cutaneous, muscular, and peritendinous nerve trunks. From the myotendinous junction the nerve fibers cross and enter the endotenon septa. In the paratenon, nerve fibers form rich plexuses and send branches that penetrate the epitenon. Most nerve fibers do not actually enter the tendon proper, but terminate as nerve endings on its surface.

The nerves of tendons are composed of myelinated, fast-transmitting Aα- and Aβ-fibers and unmyelinated, slow-transmitting Aγ-, Aδ-, B- and C-fibers. The nerve endings of myelinated fibers (Aα, Aβ) are type I-III specialized mechanoreceptors, whose main function is to mediate physical energy (pressure, tension) into afferent nerve signals. The unmyelinated nerve endings of Aγ-, Aδ-, and C-fibers are type IVa fibers, so called nociceptors. These nerve endings mediate deep tissue pain and hyperalgesia that are typical features of tendon pain. The nerve endings of B-fibers, which are autonomic, consist of type IVb fibers mainly located in the walls of small arteries, arterioles, capillaries, and postcapillary veins and exert vasomotor actions.

Over the last decade, the peripheral nervous system in addition to classical functions such as nociception and vasoactivity, has been found to also participate in the regulation of a wide variety of efferent actions on cell proliferation, cytokine expression, inflammation, immune responses and hormone release [12,27,33,57,61,64,67]. The paradoxical "efferent" role of afferent nociceptive fibers as suggested by Bayliss [11] more than one century ago is now widely recognized. So far, however, the innervation and neuronal regulation of periarticular tissues, and especially tendons, have received little attention. In particular, this applies to the specific neuronal mediators, i.e. the signal substances.

The mediators of the nervous system act through 2 principally different ways:

1) With fast transmitters, i.e. classical neurotransmitters (monoamines, acetylcholine, amino acids), which directly effectuate muscle contractions or afferently relay information on painful stimuli.
2) With a family of slow transmitters, neuropeptides, which slowly regulate physiological functions in the central as well as peripheral nervous system.

Neuropeptides

Neuropeptides act as chemical messengers and regulators in the central and peripheral nervous systems. They differ from classical neurotransmitters in several respects. Peripheral neuropeptides are synthesized in the cell bodies, i.e. the dorsal root ganglia (sensory) and the sympathetic chain (autonomic), and transported distally. In contrast, classical neurotransmitters are synthesized in the axon terminals, thus exerting their effects more locally. Synthesis and turn-over of classical transmitters are more rapid than those of neuropeptides leading to more long-lasting regulatory effects of the neuropeptides. Moreover, several neuropeptides are coreleased, also together with classical transmitters [34], which offers the opportunity of a variety of functional interactions. The effects of neuropeptides and classical transmitters are elicited by different mechanisms, resulting in direct effects of classical transmitters, while neuropeptides act in a regulatory, "supervising" fashion.

Several neuropeptides have been identified in both the central and peripheral nervous system. So far, however, research on the occurrence and functions of neuropeptides in tendons has been very limited. Those hypothetically are important for nociception and tissue homeostasis in tendon can be classified in 3 groups; sensory, opioid and autonomic, according to their function and original nerve fiber type finding.

Sensory Neuropeptides

Sensory primary afferents, C- and Aδ-fibers contain substance P (SP) claimed to transmit nociceptive signals [35,40,65]. Calcitonin gene-related peptide (CGRP) coexists with and potentiates the effect of SP [56,74,77]. Both SP and CGRP have also been shown to exert proinflammatory effects such as vasodilation and protein extravasation [13,47,53]. In the periphery, release of SP leads to sensitization of surrounding primary afferents by enhancing cellular release of prostaglandins, histamines and cytokines [63,72]. Recently, however, SP also directly stimulates nociceptor endings [71]. CGRP, often colocalized with SP in unmyelinated C fibers, facilitates the release of SP and delays SP degradation in the spinal cord, thereby potentiating the nociceptive effect [38,62,77].

Sensory nerve fibers, interestingly, also seem to contain peptides with anti-nociceptive and anti-inflammatory effects counteracting the effects of SP and CGRP. Thus, galanin (GAL), somatostatin (SOM) as well as opioids, all of which occurring in primary afferents, inhibit inflammation and nociception [17,20,28,68,78]. These anti-nociceptive peptides probably exert their modulatory effect through inhibition of SP release [15,25,78,79].

Opioid Neuropeptides

The opioid neuropeptides and their receptors are, in similarity with sensory neuropeptides, produced by primary sensory neurons (dorsal root ganglia) and transported centrally and peripherally.

The endogenous opioid peptides consist of 3 families (enkephalins, dynorphins, and endorphins), which contain several biologically active products, e.g. Met-enkephalin-Arg-Pro (MEAP) and dynorphin B (DYN B), that exert physiological actions by interacting with opioid receptors. Enkephalins are thought to be the ligands for the δ-opioid receptor, and dynorphins for the κ-receptor. Recent studies identified endomorphins as endogenous ligands for μ-opioid receptors in addition to endorphins and enkephalins. A fourth opioid receptor was also demonstrated. This is genetically closely related to the others receptors and responds to the endogenous agonist nociceptin.

The endogenous opioids seem to provide a peripheral anti-nociceptive system. Thus, it was recently reported that intra-articular morphine after arthroscopic procedures had a significant analgesic effect in a dose-response manner. Notably, morphine inhibits SP release from peripheral sensory nerve endings [15,79]. Opioid receptors are therefore not only confined to the CNS, but also occur in the periphery, implication that pain can be inhibited at a peripheral level [29]. Indeed, opioid receptors have been demonstrated in peripheral sensory nerve terminals of the skin [19,66,73]. As for tendons, the neuronal occurrence of endogenous opioids and receptors, had, until recently, not been explored.

Autonomic Neuropeptides

Autonomic B-fibers in the periphery contain several mediators with sympathetic and parasympathetic effects. Neuropeptide Y (NPY) found in sympathetic fibers is a potent vasoconstrictor. It often co-exists with the classical transmitter noradrenaline (NA) potentiating the vasoconstrictive action of the latter [45]. In parasympathetic nerve fibers, vasoactive intestinal polypeptide

(VIP) has been shown to be a potent vasodilator [44]. In addition to the well established vasoactive role of VIP, other important effects have been reported over the last years. Thus, VIP has been implicated in the regulation of immune cells and the expression of cytokines and growth factors.

Neuropeptides in Tendons

As information on neuropeptide prevalence in connective tissue was largely unexplored, we studied the neuropeptide occurrence in tendons as compared to ligaments [1]. With a combined approach based on radioimmunoassay (RIA), immunohistochemistry (IHC) and high performance liquid chromatography (HPLC), 3 main classes of neuropeptides, autonomic, sensory and opioid in normal rat Achilles tendon and medial collateral ligament have been detected. The combined quantitative and morphologic analyses have demonstrated 12 neuropeptides; sensory (SP, NKA, CGRP, GAL, SOM); and opioid (LE, ME, MEAP, MEAGL, nociceptin), autonomic (NPY, VIP) in tendons [1].

Occurrence and Levels of Neuropeptides

Sensory Peptides

Overall, several studies have disclosed the occurrence of sensory neuropeptides in both animal and human tendons [4,24,43]. In tendons, sensory neuropeptides with nociceptive and pro-inflammatory effects (SP and CGRP) as well as others (GAL, SOM), which are known to modulate these effects, are present. Thus, the relative concentrations of sensory mediators and modulators could suggest physiological nociceptive thresholds.

The concentrations of SP, CGRP vs. GAL were about 4 times higher in tendons compared to ligaments [4], which might reflect a tissue specific vulnerability to pain (Figure 27-1A). These levels can change in response to outer or inner stress [33], possibly explaining why pain syndromes in tendons are more common than in ligaments (Figure 27-1A).

In fact, increased levels of sensory neuropeptides are involved in painful and inflammatory conditions. Several studies have demonstrated increased levels of sensory peptides in patients with rheumatoid arthritis [50] and in tendons of rats with experimentally induced arthritis [14]. One report also showed increased levels of SP to correlate with the pain caused by rotator cuff disease [24]. Other studies demonstrated increased levels of the neurotransmitter glutamate in painful patellar and Achilles tendons of patients with tendinopathy [8,9], indicating increased neuronal activity. Glutamate is known to exist

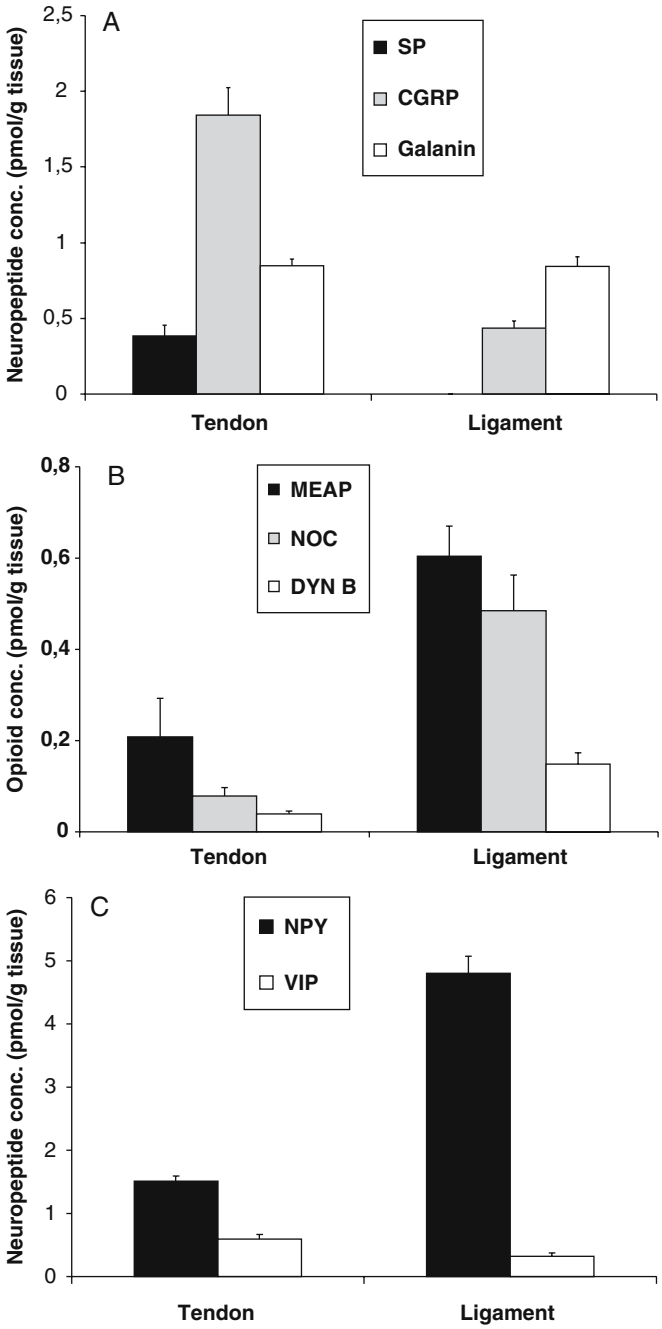


FIGURE 27-1. Radioimmunoassay tissue concentrations (pmol/g) of sensory (SP, CGRP and GAL) (A), opioid (MEAP, N/OFQ and DYN B) (B), and autonomic (NPY and VIP) (C) neuropeptides in the Achilles tendon and collateral ligaments of rat knee (mean ± s.e.m.). (Adapted from Ackermann WP, Finn A, Ahmed M. Sensory neuropetidergic pattern in tendon, ligament and joint capsule. A study in the rat. *Neuroreport.* 1999; 10(10): 2055–60. Reproduced from Ackermann et al. Autonomic innervation of tendons, ligaments and joint capsules. A morphologic and quantitative study in the rat. *J Orthop Res* 2001; 19, 372–8, with permission from the Orthopaedic Research Society. Reproduced with permission from Ackermann et al. An Opioid System in Connective Tissue: A Study of Achilles Tendon in the Rat. *J Histochem Cytochem* 2001;49:1387–96.)

peripherally and to interact with SP in nociception [18]. SP potentiates the effect of glutamate [18,42], which was also demonstrated in Achilles tendons of patients with tendinopathy [7].

The occurrence of sensory neuropeptides in tendons complies with nociceptive effects, possibly in combination with traditional neurotransmitters, and the neuropeptide levels indicate a vulnerability to develop painful disorders.

Opioid Peptides

A peripheral neuronal source of anti-nociception to modulate the sensory system could be the endogenous opioid neuropeptides. Notably, data on opioids in the peripheral nervous system and specifically tendons are quite scarce. However, an opioid system in the Achilles tendon of rats was recently detected (Figure 27-1B) [2]. This was the first observation on the occurrence of opioids including nociceptin in periarticular tissues. The results clearly demonstrated the existence of opioid peptides (enkephalin and nociceptin) in the tendon.

The physiological role of enkephalins like MEAP can be assumed to be anti-nociceptive [17,46], anti-inflammatory [31,39], vasodilatory [23,52], immunosuppressive [16] and trophic [75,80]. Notably, the release of SP from afferents in the cat knee joint is inhibited by intra-articular enkephalin-analogue injections [79]. Also, nociceptin can reduce mechanosensitivity in the rat knee joint through inhibition of SP release [48,49].

The lower concentrations of MEAP and nociceptin in tendons compared to ligaments (Figure 27-1B) could reflect a greater susceptibility to pain and inflammation, in particular when considering also the high levels of SP found in tendons. The combined quantitative data obtained suggest a balance between nociceptive and anti-nociceptive peptides under normal conditions. This balance may be altered in pathological conditions.

Autonomic Peptides

The presence of autonomic peptides has been demonstrated in tendons of both animals [5] and humans [43]. The autonomic peptides in sympathetic (NPY) and parasympathetic (VIP) nerve fibers exert opposite effects in the regulation of vasoactivity.

One study showed that the concentration of NPY compared to VIP was 15 times higher in ligaments and twice as high in tendons (Figure 27-1C). The observation would seem to reflect that the sympathetic tone is higher than the parasympathetic in tendons and ligaments. Such a difference between tissues may be assumed to be of importance for blood-flow, and hypothetically for healing capacity, possibly also for susceptibility to degeneration and injury. Notably, ligaments are more prone to rupture than tendons [76].

Altogether, quantitative analysis of tendons has demonstrated autonomic, sensory and opioid peptides presumed to be involved in nociception, inflammation and vasoactivity. The relative levels of counteracting neuropeptides, may represent the tissue homeostasis of different functions and, possibly the susceptibility to external stress. In fact, increased levels of pro-nociceptive sensory mediators have been shown in painful tendon conditions.

Morphological Distribution of Neuropeptides

Morphological studies by immunohistochemistry have verified the neuronal occurrence of 11 neuropeptides.

Sensory Fibers

Nerve fibers immunoreactive to SP, CGRP, NKA, GAL and SOM were consistently identified in the Achilles tendon of the rat [4]. The highest fiber density was observed in the surrounding tissues, i.e. the paratenon and loose connective tissue (Figure 27-2). The ratio of vascular vs non-vascular fibers was higher in the surrounding loose connective tissue than in the paratenon, which exhibited a large number of non-vascular free nerve endings (Figure 27-2C).

Thus, the abundance of immunopositive vascular fibers in the surrounding loose connective tissues may reflect an important role in the regulation of blood flow to the proper structures. Both SP and CGRP, in particular the latter, are potent vasodilators [13]. In addition, they have pro-inflammatory effects, e.g. by enhancing protein extravasation and leukocyte chemotaxis. The occurrence of sensory free nerve endings unrelated to vessels predominantly seen in the paratenon suggests a nociceptive role.

Opioid Peptides and Receptors

Morphological studies demonstrated the neuronal presence of several enkephalins, i.e. LE, ME, MEAP, and MEAGL, in peripheral nerve fibers of the rat Achilles tendon (Figure 27-3D) [2]. All 4 enkephalins predominantly occurred in the loose connective tissue, the paratenon and musculotendinous junction, and no enkephalins were found in the tendon proper. Hypothetically, this difference in anatomical distribution might suggest that regulation of painful disorders of the Achilles tendon mainly occurs in the surrounding tissues, which during normal condition also harbor the sensory and autonomic neuropeptides.

The existence of an opioid system in connective tissues, as demonstrated by neuronal immunoreactivity to enkephalins, was supported by opioid receptor studies

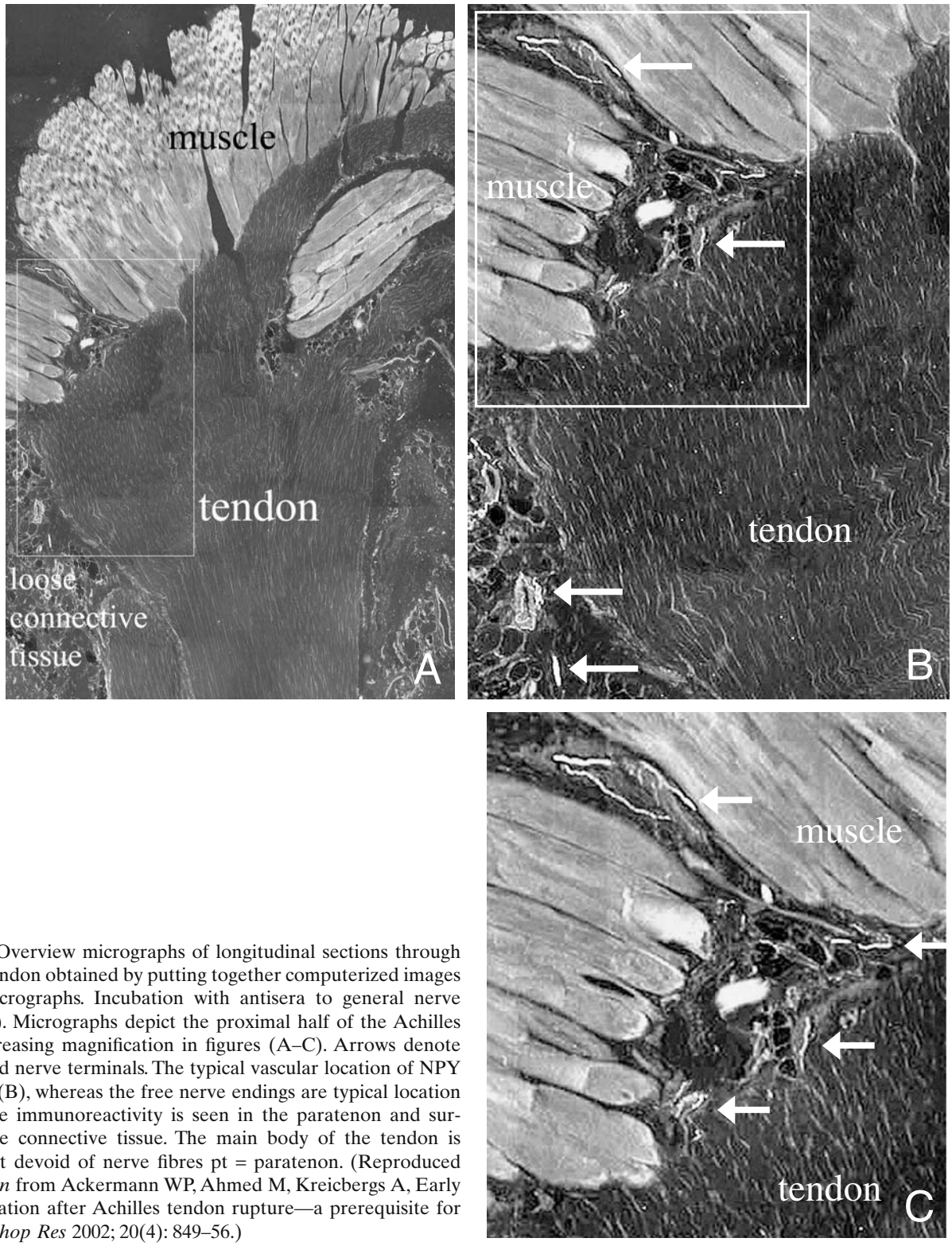
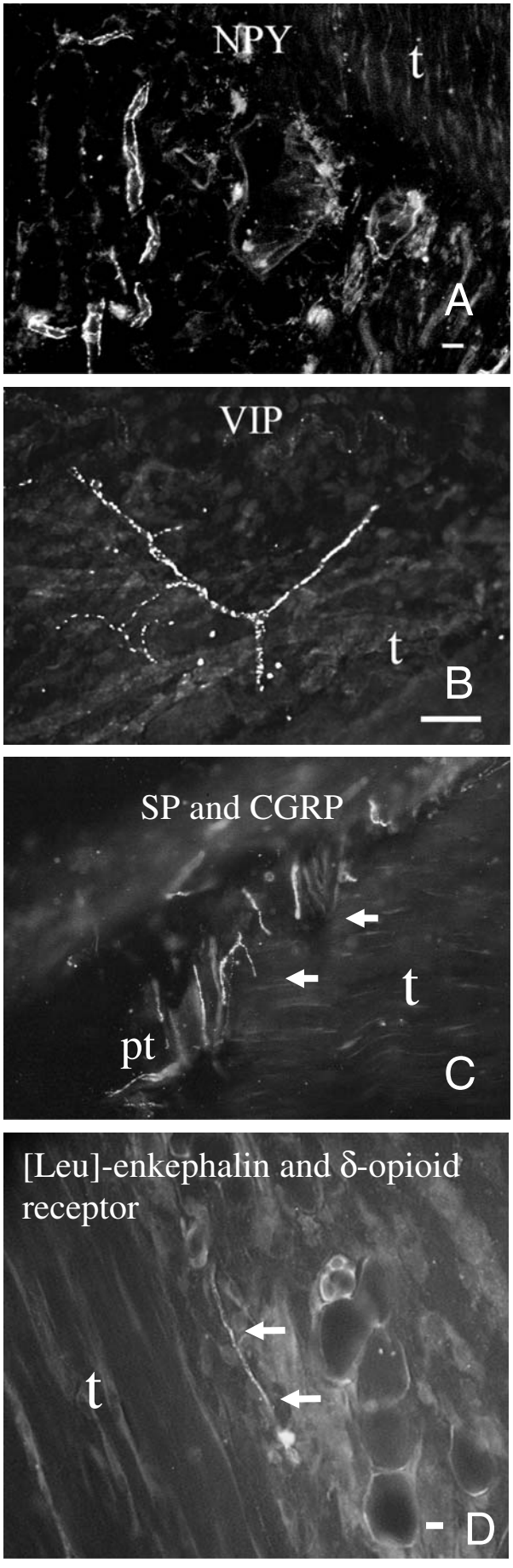


FIGURE 27-2. Overview micrographs of longitudinal sections through the Achilles tendon obtained by putting together computerized images of smaller micrographs. Incubation with antisera to general nerve marker (PGP). Micrographs depict the proximal half of the Achilles tendon at increasing magnification in figures (A–C). Arrows denote varicosities and nerve terminals. The typical vascular location of NPY is depicted in (B), whereas the free nerve endings are typical location of SP (C). The immunoreactivity is seen in the paratenon and surrounding loose connective tissue. The main body of the tendon is notably almost devoid of nerve fibres pt = paratenon. (Reproduced *with permission* from Ackermann WP, Ahmed M, Kreicbergs A, Early nerve regeneration after Achilles tendon rupture—a prerequisite for healing? *J Orthop Res* 2002; 20(4): 849–56.)

based on binding assays and immunohistochemistry [2]. Of the 3 opioid receptors (δ-,κ-,μ-) studied, however, only the δ-opioid receptor (DOR) could be detected by immunohistochemistry (Figure 27-3D). Double staining disclosed coexistence of each of the enkephalins with DOR in the nerve fibers (Figure 27-3D), which is in accordance with other studies suggesting that enkephalins are the main ligands for DOR [21]. DOR exerts a potent inhibitory effect on SP release [30,79]. There are several reports demonstrating that treatment



with delta opioid agonists in the periphery elicit both anti-inflammatory and anti-nociceptive effects in models of inflammation [55,69,81]. Presumably, the coexistence of enkephalins and DOR in vascular nerve fibers reflects inhibition of neurogenic pro-inflammatory actions, whereas the co-existence in free nerve endings reflects inhibition of nociception.

The present findings suggesting a neuronal source of opioids in the periphery probably reflect an antinociceptive system in tendons, which may be exploited in the therapeutic setting by drugs acting selectively in the periphery.

Autonomic Fibers

Both sympathetic (NPY, NA) and parasympathetic (VIP) fibers were identified in the tendon [5]. The autonomic fibers were mostly observed as networks around blood vessels located in the loose connective tissue around the tendon proper (Figure 27-2). Overall, these observations reflect that the regulation of blood flow to tendons predominantly occurs in the adjacent loose connective tissue.

Altogether, there seems to exist a complex neuropeptidergic network in tendons with a specific ratio of potentiating and inhibitory mediators. The observations may well reflect unique tissue requirements under normal conditions including the susceptibility to stress. The most conspicuous findings pertained to the abundance of sensory fibers in the surrounding tissues of the tendon, whereas the tendon proper, notably, was almost devoid of nerve fibers (Figure 27-2). This would seem to reflect that the neuronal regulation of tendons highly depends on the innervation of the surrounding tissues.

FIGURE 27-3. Immunofluorescence micrographs of longitudinal sections through the Achilles tendon after incubation with antisera to NPY (A), VIP (B) and doubble staining (co-localization) of SP and CGRP (C), LE and DOR (D). The NPY-positive fibres are arranged as nerve terminals in the vessel walls. VIP-positive nerves are arranged as a "fence", surrounding the main body of the tendon, of small varicosities in the paratenon. Co-existence of SP and CGRP is evident in the paratenon, indicating possible pro-inflammatory actions. The immunoreactivity displaying co-existence of LE and DOR is seen as free nerve endings in the paratenon, which indicates a potential peripheral anti-nociceptive system. t = tendon tissue; Pt = paratenon; Bar = 50 µm. (Adapted from Ackermann WP, Finn A, Ahmed M. Sensory neuropetidergic pattern in tendon, ligament and joint capsule. A study in the rat. *Neuroreport* 1999; 10(10): 2055–60. Reproduced from Ackermann et al. Autonomic innervation of tendons, ligaments and joint capsules. A morphologic and quantitative study in the rat. *J Orthop Res* 2001;19, 372–8, with permission from the Orthopaedic Research Society. Reproduced with permission from Ackermann et al. An Opioid System in Connective Tissue: A Study oof Achilles Tendon in the Rat. *J Histochem Cytochem* 2001;49:1387–96.)

Neuronal Response After Tendon Injury

Having established the normal occurrence of nerve fibers and their expression of different neuropeptides mainly localized in the surrounding structures of the tendon, i.e. the paratenon, this section aims to explore the distribution of nerve fibers and their expression of neuropeptides after injury and during healing of tendinous tissue. In addition to cytokines and growth factors, neuropeptides in the periphery may participate in tissue repair [12,27,57,61].

Neuropeptides and Repair

Neuropeptides elicit and convey responses to stress and injury [33], responding very specifically both in the central and peripheral nervous system to peripheral inflammation and nerve injury. A number of experimental studies on arthritis have demonstrated a local increase in SP and CGRP one week after induction with adjuvans. After peripheral nerve lesion, a number of studies show that the expression of different neuropeptides follows a specific temporal pattern in accordance with the healing phases [36,59]. This would seem to reflect a regulatory role of neuropeptides in response to injury, which possibly also could play a role in tendon repair.

New Nerve Fiber Ingrowth After Injury

Both human [24,60,70] and animal studies [10,22,51,58] indicate specific nerve fiber response to tendon injury, where nerve fiber ingrowth often is associated with increased experience of pain. Our studies of tendon injury specifically addressed the question of nerve regeneration during healing of experimental Achilles tendon rupture. Nerve regeneration at different time points (1–16 weeks) was investigated by immunohistochemistry, including semi-quantification of neuronal markers for new and mature fibers [3].

In the first week after rupture, corresponding to the inflammatory phase, there was increased nerve fiber activity in the surrounding loose connective tissue. From 1 to 6 weeks after rupture (regenerative phase), there was a striking shift in neuronal occurrence from the surrounding loose connective tissue into the rupture site of the tendon proper (Figures 27-4 and 27-5), in normal conditions notably devoid of nerve fibers. The peak expression of new nerve fibers at the rupture site occurred between weeks 2 and 6, while mature nerve fibers were seen somewhat later, between weeks 4 and 6. During weeks 8 to 16 after rupture (remodeling phase), the nerve fibers decreased significantly at the rupture site (Figure 27-4). They successively returned to normal in the paratenon and surrounding loose connective tissue, reflecting the plasticity of the peripheral nervous system.

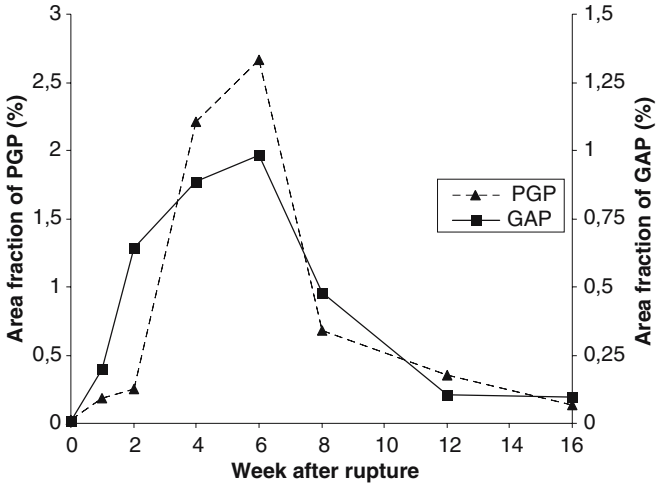


FIGURE 27-4. Area occupied by nerve fibers (%) immunoreactive to GAP (regenerating nerve fibers) and PGP (mature nerve fibers) in relation to total area, in the mid third of the tendon, over 16 weeks post rupture (mean ± s.e.m.). (Reproduced with permission from Ackermann WP, Ahmed M, Kreicbergs A, Early nerve regeneration after Achilles tendon rupture—a prerequisite for healing? *J Orthop Res* 2002; 20(4): 849–56.)

In summary, tendon injury is characterized by nerve fiber ingrowth at the rupture site, a peak nerve fiber expression during the regenerative phase, followed by nerve fiber withdrawal during the remodeling phase. The ingrowth and later withdrawal of nerve fibers in the tendon proper after rupture point towards a fundamental role of neuronal supply for tendon tissue healing. Presumably, new nerve ingrowth is a prerequisite for delivery of neuronal mediators required for tissue repair.

Temporally Orchestrated Neuropeptide Occurrence During Repair

So far there are very limited data on the peripheral expression of neuropeptides after injury of musculoskeletal tissues. Increased expression of SP and CGRP 2 weeks after injury has been observed in fracture and skin healing [32,37,41]. Grönblad et al. studied SP and CGRP expression 4 and 14 weeks after ligament rupture, and found an increase at week 4 and a decrease at week 14 [26]. Altogether, the temporal expression of neuropeptides indicates their involvement in not only the acute response to injury, but also in tissue regeneration.

Bearing this in mind, we studied the temporal expression of specific neuropeptides at different time points (1 to 16 weeks) after rupture using the same experimental Achilles tendon rupture mentioned above. The study entailed morphological and semi-quantitative analyses by immunohistochemistry of sensory (SP, CGRP), sensory modulating (GAL), and autonomic (NPY, VIP) neuropeptides [1,6].

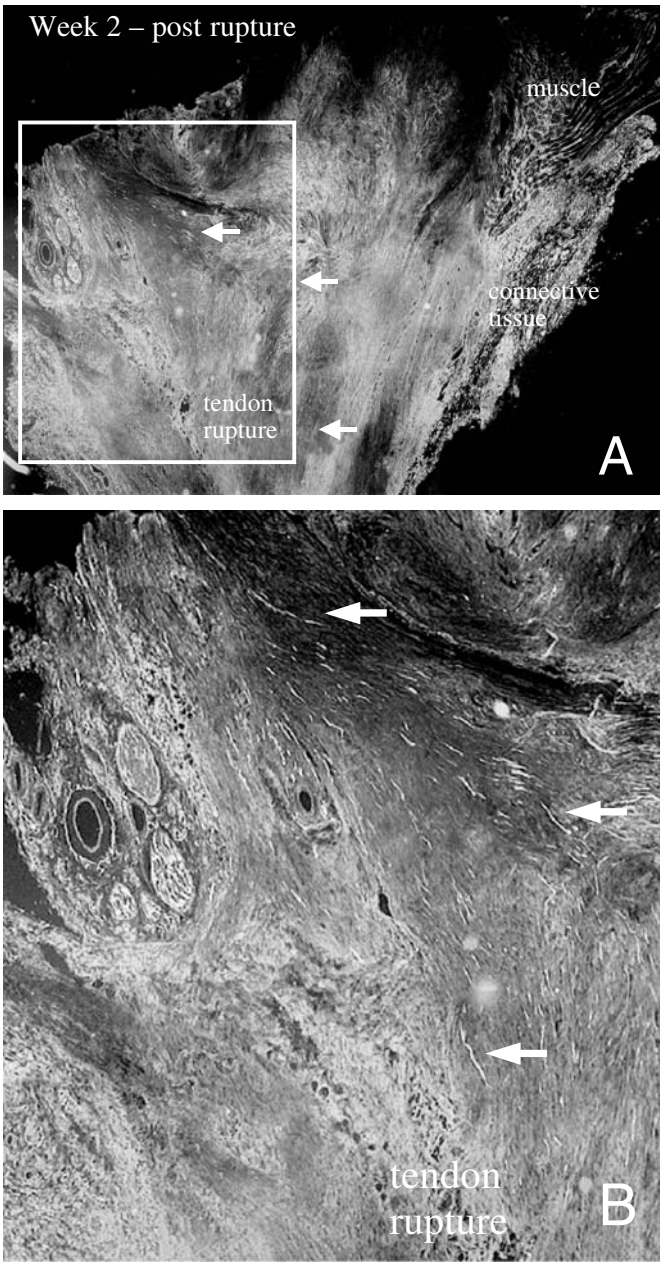


Figure 27-5. Overview micrographs of longitudinal sections through the Achilles tendon 2 weeks after rupture obtained by putting together computerized images of smaller micrographs. Incubation with antisera to a nerve growth marker, GAP-43. Micrographs depict the proximal half of the Achilles tendon at increasing magnification in figures (A–B). Arrows denote varicosities and nerve terminals. The GAP-positive fibers, indicating new nerve fiber ingrowth, are abundant in the healing main body of the tendon. Some GAP-fibers are also located in the loose connective tissue, but most are located as free nerve endings within the healing main body of the tendon. (Reproduced with permission from Ackermann WP, Ahmed M, Kreicbergs A, Early nerve regeneration after Achilles tendon rupture—a prerequisite for healing? *J Orthop Res* 2002; 20(4): 849–56.)

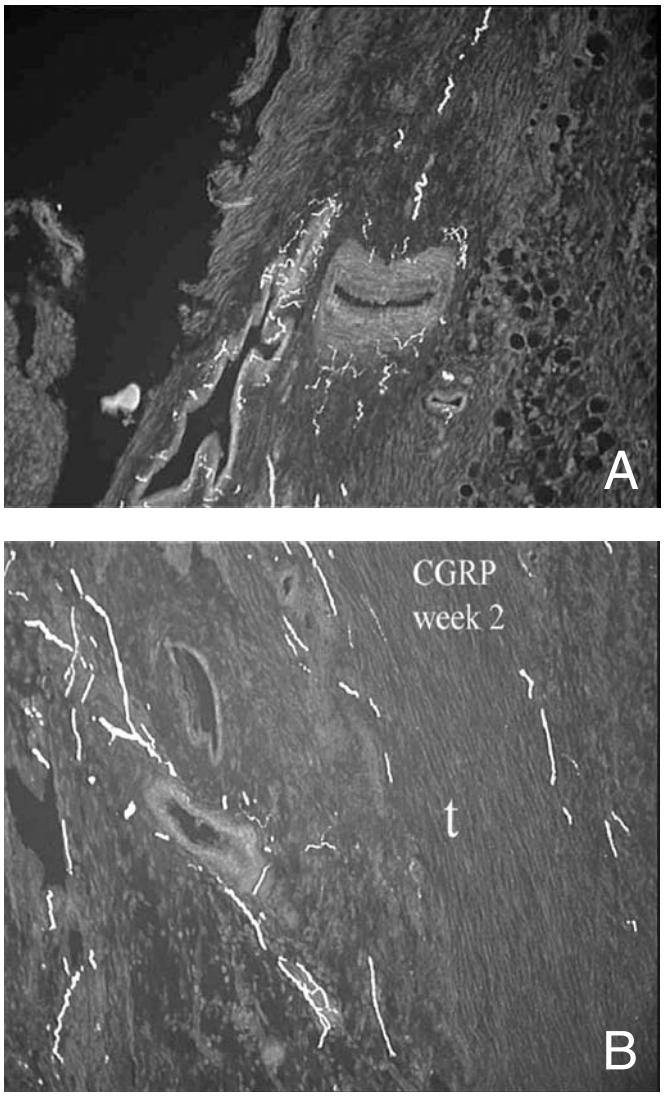


Figure 27-6. Immunofluorescence micrograph of longitudinal sections through healing Achilles tendon 1- (A) and 2- (B) weeks after rupture after incubation with antisera to CGRP. Nerve fibers immunoreactive to CGRP are seen as vascular and free nerve endings in the loose connective tissue (A). CGRP-immunoreactivity occurs mainly in the healing tendinous tissue as sprouting free nerve fibers. v = blood vessel; lct = loose connective tissue; t = main body of the tendon; Bar = 50 µm. (Reproduced from Ackermann et al. Early nerve regeneration after achilles tendon rupture—a prerequisite for healing? *J Orthop Res* 2002; 20: 849–56, with permission from the Orthopaedic Research Society.)

One week post rupture (inflammatory phase), SP and CGRP fibers were predominantly located in blood vessel walls surrounded by inflammatory cells in the loose connective tissue (Figure 27-6A). This complies with a nociceptive and pro-inflammatory role. During week 2 to 6 (regenerative phase), the expression of SP and CGRP peaked (Figure 27-7). Notably, this peak occurred at the

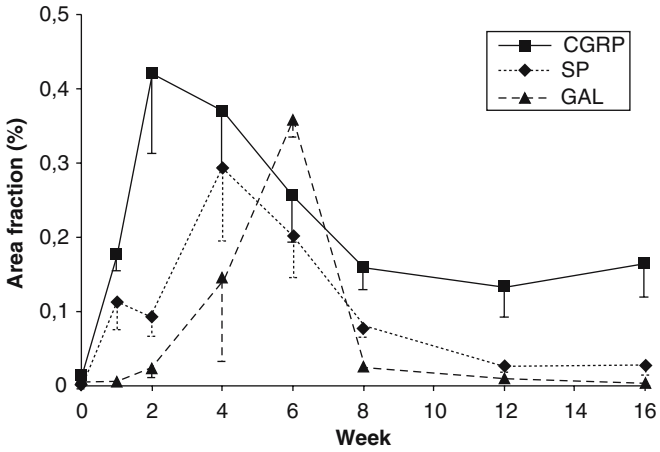


FIGURE 27-7. Area occupied by nerve fibers (%) immunoreactive to SP, CGRP and GAL in relation to total area, in the mid third of the tendon, over 16 weeks post rupture (mean ± s.e.m.). (Reproduced from Ackermann et al. Neuronal plasticity in relation to nociception and healing of rat achilles tendon. *J Orthop Res* 2003; 21, 432–41, with permission from the Orthopaedic Research Society.)

rupture site of the tendon proper, seen as free sprouting nerve endings among fibroblasts and newly formed vessels (Figure 27-6B), which may reflect a role for SP/CGRP in cell proliferation. Up to week 4, the occurrence of GAL, NPY and VIP was sparse. Subsequently, the expression of GAL, NPY and VIP increased to reach a peak at the end of the regenerative phase, around week 6, followed by their successive decrease, SP and CGRP included, until the end of the experiment (week 16) (Figure 27-7). The early appearance of SP and CGRP in tissues surrounding the tendon would seem to comply with a nociceptive and pro-inflammatory role, whereas the later occurrence at the rupture site may prove to reflect a role in cell proliferation. The emergence of GAL, VIP and NPY in the early remodelling phase may, in addition to regulation of vasoactivity, represent modulatory effects on SP and CGRP. This modulation may be required to switch from the nociceptive, inflammatory and regenerative processes to the remodeling phase.

Summary

Tendinous tissues are supplied with a complex network of neuronal mediators, which may be involved in the regulation of nociception, vasoactivity, and inflammation. In response to injury, the expression of neuropeptides is significantly altered in a temporally orchestrated manner, suggesting a well synchronized mechanism in nociception and tissue repair.

The relevance of the present findings pertains to the possibility of intervening in different efferent mechanisms of the peripheral nervous system, which presumably are implicated in a wide variety of functions such as vasoactivity, nociception, inflammatory responses, and regeneration. Specific neuronal intervention, however, presupposes that the innervation of the musculoskeletal system according to specific mediators is clarified. Tendons are supplied with a complex peptidergic network, which presumably takes part in maintaining tissue homeostasis. Ingrowth of new nerves seems to be a fundamental feature of tissue repair.

Whether neuronal mediators could be utilized in tissue engineering has so far not been explored. As for pharmacotherapy, it may prove that this can be targeted to specific neuronal mediators to enhance or inhibit their effects in painful conditions of the tendons.

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28
The Use of Growth Factors in the Management of Tendinopathies

Louis C. Almekinders and Albert J. Banes

Introduction

Tendinopathies present a difficult therapeutic problem for the patient as well as the health care professional because their etiology and management are uncertain [1]. Although many forms of management have been advocated, current treatment strategies are not effective because they do not definitively resolve the disease. Pharmacological management with non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids can result in some pain relief but the relief is often temporary. Ideal management should have minimal side effects. The currently used corticosteroids have frequently been associated with side effect is such as depigmentation, poor wound healing and even complete tendon rupture. Finally, the ideal treatment should accomplish its goal in a relatively short period of time with little discomfort or disability to the patient. Surgery can definitively treat tendinopathy. However, the recovery is associated with pain and discomfort, and recovery is often protracted. Many of our current management methods do not fulfill the criteria of ideal treatment, therefore the search for such a treatment continues.

Results of many studies suggest a poor or inadequate healing response in tendinopathies. Part of the search for new treatments has been focused on methods to start or stimulate a healing response. This is fundamentally different than the thought behind the use of NSAIDs and corticosteroids. These drugs are aimed at the symptoms that result from the injury or problem rather than the healing response. Symptoms such as pain and swelling can be interpreted as inflammatory aspects of the tendinopathy. Treatment with NSAIDs and corticosteroids can counteract these responses. On the other hand, the inflammatory response can be viewed as the first physiologic step in the healing of a tendon, followed by cell migration into a wound and matrix maturation. However, tendinopathies may not evoke a sufficient inflammatory response to elicit an adequate repair response. Inhibition of inflammation with NSAIDs and corticosteroids will manage some of the symptoms, but may not improve and may even inhibit the eventual healing response. More recent research has been focused on agents that may affect tendinopathies by directly acting on the healing response.

Growth factors such as platelet-derived growth factor (PDGF-AA, BB, or AB), insulin-like growth factor (IGF-I and II), transforming growth factor beta (TGF-b), epidermal growth factor (EGF), fibroblast growth factors (FGF 1,2) and bone morphogenetic proteins (BMPs) represent a group of substances that can act in such a manner. Growth factors may be produced locally by cells in areas of injury, growth and repair, or may be delivered by blood. Since their discovery, they have been implicated in numerous responses where they modulate cell migration, replication, matrix synthesis, and cell transformation. Exogenous supplementation of these factors in failed healing responses, such as in resistant tendinopathies, may lead to a definitive healing response.

The Biology of Growth Factors in Tendons

The existence of factors with stimulatory properties on nerve growth, epidermal cell growth [2] and sulfate incorporation in cartilage [3] was demonstrated in the 1950s and 1960s. Research in the subsequent decades led to the identification of a significant number of polypeptides that had pronounced effects on cell division, matrix synthesis and many other basic cellular functions. Often these factors were named after their cell or tissue source, or their first observed effects. This led to a variety of names such as platelet-derived growth factors, bone morphogenetic protein, transforming growth factor-beta, etc. Only more recent research has led to their biochemical identification of their cDNA and mRNA sequences, primary structure and determination of their effects on cells and tissues.

More recent research has led to the detection of a much more complex system in which these growth factors work. These factors may function in positive or negative feedback loops, have multiple effects depending on dose and act in synergy when given with other factors. Growth factors are responsible for a complex communication system not only from cell to cell but also from exogenous stimuli to cells and as intermediaries between hormones and cytokines. Growth factors can inhibit or stimulate cell migration, division, matrix synthesis and degradation, angiogenesis, mineralization and many more processes. The effect of a particular growth factor on a cell is dependent on the cell type and receptor expression. In some cases, a tenocyte will respond differently than a chondrocyte, within one cell type a different response to a growth factor can be seen, and young, growing cells may respond differently than mature, nondividing cells. Finally, differences in the local concentration of growth factor and the presence of other factors may result in profoundly different effects. Some factors may be able to amplify others, whereas others may be inhibiting. With this in mind, we are only starting to understand the various effects of growth factors and their complex interactions on tendon cells.

Growth factors exert their effects on cells through specific receptors. If these receptors are absent or blocked, the growth factors will be ineffective. For instance, the PDGF receptors must dimerize to signal inwardly (outside-in signaling) to initiate the internal response cascade once the growth factor binds to its receptor. Once the growth factor polypeptide binds to the receptor, this ligand-receptor interaction activates the intracellular domain on the receptor and a biochemical signal is transduced into the cell. The signal transduction can take place in various ways. Generally, this signaling pathway appears to be a cascade of phosphorylation of different proteins [4]. At the nuclear level, binding of transcription factors to gene sequences activate gene transcription (see Figure 28-1). This results in the generation of messenger RNA that is transcribed into protein. The protein may have one of many functions such a matrix component, an enzyme that regulates a metabolic event, a promoter or suppressor protein that promotes or suppresses transcription of other genes, etc. This is thought to be one of the most common pathways through which growth factors evoke a cellular response. A brief review of the most commonly studied factors and their effects on tendon tissue and cells will follow.

Bone morphogenetic proteins of BMPs are a group of TGF-b superfamily factors that stimulate bone formation (BMP-2) but also stimulate tendon cell mitogenesis (BMP-13). The bone formation is promoted by recruiting precursor cells and stimulating enchondral ossification [5].

Insulin-like growth factor, or IGF, is named after the hypoglycemic effect it has upon intravenous administration. However, IGF has pronounced effects on mitogenesis of several cell types [6]. IGF is often subdivided in to classes: IGF-I and IGF-II. IGF-I has direct mitogenic effects, but also appears to mediate the effect of growth hormone. IGF-II is associated with the regulation of fetal growth. The stimulatory effects of IGF-I have been shown in many cell types including cartilage, bone, muscle and tendon cells. Besides a mitogenic effect, it can also stimulate selected components of matrix synthesis. Recent work shows that it is also produced by tenocytes [7]. It induces tendon cell migration, division, and matrix expression [8,9].

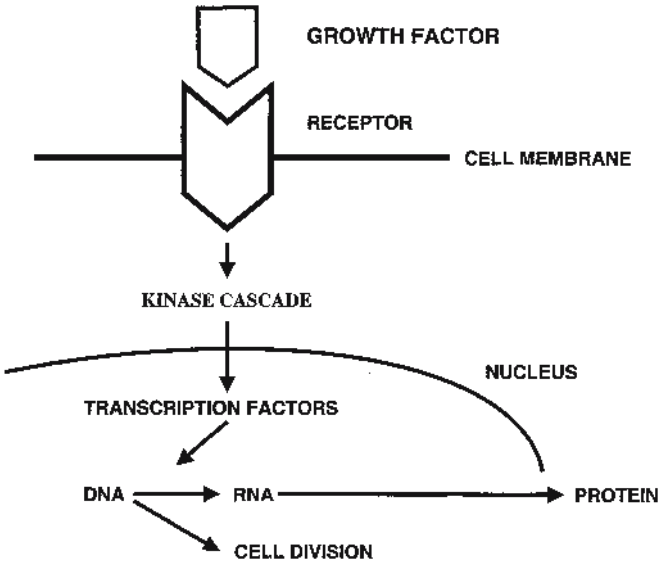

FIGURE 28-1. Schematic drawing of mechanism of action through which growth factors affect cellular events.

Platelet-derived growth factor, or PDGF, was first isolated from platelets, but can be produced by different cells such as smooth muscle cells [10]. Some isoforms of PDGF, such as PDGF-BB, have stimulatory effects on both cell division as well as matrix synthesis. It appears that PDGF hold particular promise in combination with other growth factors. Its effects are noted or even amplified in combination with other factors such as IGF-I. Tendon cells express the receptor for PDGF but do not normally express PDGF itself [7]. PDGF-BB stimulates robust tendon epitenon and internal fibroblast cell migration, particularly in concert with IGF-I [11]. PDGF also stimulates cell division, particularly when combined with IGF-I [8,9]. These two growth factors act synergistically with cyclic tension to stimulate cell division. Moreover, serum, which contains both PDGF and IGF-I, stimulates cells in whole tendon both mitogenically and matrigenically, and synergistically with cyclic load [12]. This will be discussed in more detail in the following section.

Transforming growth factor beta or TGF-β is a group of polypeptides related to the BMPs. Originally, TGF-β

was thought to be related to the cellular transformation to neoplastic growth. More recent research, however, has made clear that TGF-β can have numerous physiologic effects [13]. It appears closely tied to the expression of a differentiated phenotype in many cell lines. Particularly, the mesenchymal precursor can be influenced by TGF-β. Tendon and ligament formation has been tied directly to factors belonging to the TGF-β superfamily [14]. Proliferation, matrix synthesis and differentiation have also been affected in both chondroblasts and osteoblasts. Whether this is an inhibitory or stimulatory effect depends on the stage of differentiation, presence of other growth factors and assay system used. TGF-β is a weak stimulator of tendon cell migration and mitogenesis but can stimulate robust expression of matrix [15].

Fibroblast growth factors (FGF 1,2) contain a group of heparin-binding proteins. They are named after their mitogenic effects on fibroblasts, and are also found to influence osteoblast precursors and chondrocytes [16]. FGF receptor mutation has been in implicated in a certain form of dwarfism. Two main forms of FGF have been identified: FGF-1 (acidic FGF) and FGF-2 (basic FGF). Both have shown promise in stimulation of new bone formation. FGF 1 and 2 are weak mitogens for tendon cells [15].

Cytokines in Tendon Cells and Tissue Responses

Similar to growth factors, cytokines influence many cellular processes. Although they are more commonly associated with diseased states, they may have physiologic functions and could be considered for therapeutic use if their actions are clearly defined. Results of recent studies indicate that cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α) can stimulate metalloproteinase expression in tendon cells (MMP-1,2,3 and 13) [17,18,19]. Inflammatory cytokines such as IL-1β and TNF-α elaborated by lymphocytes and macrophages can stimulate tendon cells to produce interstitial collagenase (MMP-1), gelatinase (MMP-2), stromelysin (MMP-3) as well as MMP-13 which can activate other MMPs to degrade collagens and aggrecans [18]. Moreover, IL-1β and TNF-α can elicit COX-2 expression and PGE2 release from stimulated tendon cells. The latter scenario may involve one of the instigating factors that initiate tendinopathy, although it is not clear why, in overuse tendinopathy, there seems to be no evidence of pro-inflammatory substances in the affected tendon by the time patients come under the care of a physician. Hence, the use of MMP inhibitors and NSAIDs may inhibit the matrix destructive cycle by blocking cyclooxygenase-2 and MMP activity.

The Use of Growth Factors in Tendon Pathology

The use of growth factors in soft tissue problems remains largely experimental and has been restricted to *in vitro* studies and animal models. In bone research, however, the first clinical studies on the use of bone morphogenetic protein (BMP) have been reported. Encouraging results have been reported with use of BMP in spinal fusion [20] and lower extremity osteotomy [21].

Several *in vitro* studies have been performed to determine the effects of growth factors on tendon cells. Gauger et al. tested the effects of epidermal growth factor, insulin and transferrin on avian tendon cells [22].

Both cell division and collagen synthesis were stimulated by these factors. The level of stimulation was similar to the effects seen from 10% serum as is commonly used in *in vitro* studies to maintain cell growth and matrix synthesis.

Banes et al. investigated the effects of PDGF-BB and IGF-I in conjunction with mechanical stimulation on avian tenocytes [9]. The tenocytes were first separated in tendon epitenon surface cells (TSC) and internal tenocytes. These cell types expressed different markers, had different growth rates and responded differently to growth factors, PGE2 and PTH [12,23]. PDGF-BB clearly stimulated TSC synergistically with mechanical load and IGF-1. PDGF-BB also stimulated TIF in a less dramatic fashion. IGF-1 with mechanical load only modestly stimulated both types of tenocytes. In a subsequent experiment, Banes et al. found that PDGF-BB was able to induce expression of novel genes in conjunction with load. IGF and TGF-β were clearly less effective. The stimulatory effect of PDGF on tenocytes and tissues has been confirmed in several other studies. Spindler et al. documented a mitogenic response of sheep patellar tendon to PDGF-AB. In addition, elevated PDGF levels have been found in healing tendon tissue [24].

FGF also has received some attention in research studies. Basic FGF addition to rat patellar tenocytes resulted in a proliferative response [25]. However, in studies of injured and non-injured tendon, higher levels of bFGF expression were found in normal tendon compared to injured tendon [26]. This may suggest that bFGF does not play a major role in the tendon healing response. This is supported by the fact that Kang et al. were unable to document a significant response from FGF in rabbit flexor tendon culture experiments [27].

Clinical use of growth factors in tendon problems has not yet been reported. One of the issues to be resolved is how to administer the growth factors in a reliable delivery system and assure that they maintain potency at the injection site. Oral or systemic injection of a growth factor are not favored, however, and direct, local administration into the tendon is a logical route. This could be

accomplished in several ways. In a pilot study, we utilized direct administration of growth factors in a patellar tendinopathy lesion. To assure deposit of the factor into the abnormal tissue, real-time ultrasonography was used. With a sterile ultrasound head in place, a needle was advanced directly into the hypoechogenic area (see Figure 28-2). Once the placement was confirmed by ultrasound at orthogonal angles the factor was injected. Post-injection, the ultrasound picture confirmed the presence of the injected fluid in the lesion. In a pilot study 6 patients were injected in this manner. In order to obtain injectable factor, venous blood was obtained from each patient prior to the injection. Platelets were isolated from this blood and injected as a 1-milliliter suspension under ultrasound monitoring. Injection of platelets directly in a collagenous structure will result in platelet degranulation. PDGF and other growth factors and cytokines are released in the affected area. Two out of 6 patients had complete relief of their symptoms, two had partial relief and two were not improved with 2 to 3 months of treatment. No side effects were seen other than some soreness at the injection site. One patient with bilateral problems had a corticosteroid injection in the contralateral tendon. He obtained immediate relief in the steroid-injected side but pain recurred after six weeks. In the platelet-injected side no immediate relief was noted but symptoms started to resolve at 6 to 8 weeks post-injection and eventually were relieved. A study of pre- and post-injection MRI images revealed complete resolution of the lesion (see Figure 28-3). More controlled studies are needed before definitive conclusions can be drawn from these results.

Another method of growth factor administration would involve the use gene therapy techniques to express

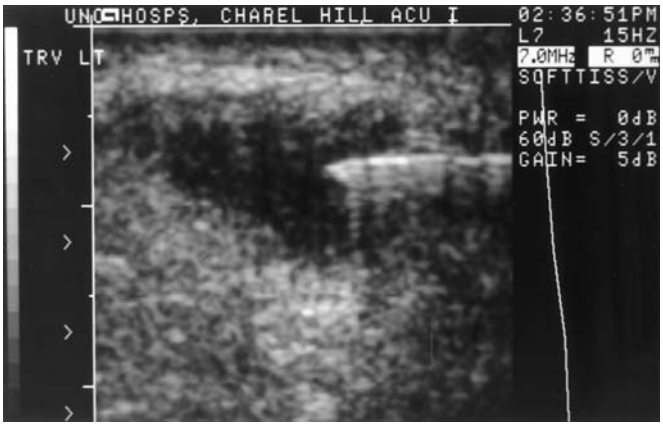

Figure 28-2. Injection of factor in area of the patellar tendon (T) near the insertion of the patella affected by insertional patellar tendinopathy under ultrasonographic control. Tip the needle (arrow) is advanced into the hypoechogenic area (*).

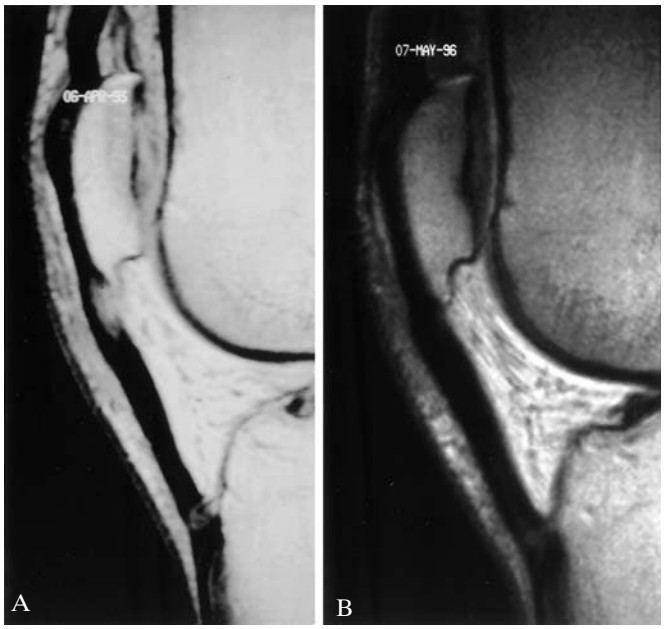

Figure 28-3. Preinjection MRI (A) and post-injection MRI (B) of patellar tendinopathy with resolution of the tendon lesion (arrow). T represents the patellar tendon and P the patella.

the gene [28]. Plasmid DNA with a sequence coding for a given factor can be expressed in tendon cells. The gene or segment of DNA can be transferred in different ways. With a direct, *in vivo* transfer, the DNA is incorporated in a vector, usually a plasmid or nonreplicating virus. The virus or plasmid is administered to the patient and allowed to infect the local cells. The local cells host the plasmid DNA and selected gene sequence and express the growth factor gene. Expression is generally low and transient, but recent data indicate that expression for as long as two months is possible. The *in vivo* technique is simpler but involves injection of virus particles. The ex-vivo technique is more demanding and requires the harvest and culture of cells from the patient. The cells are infected and then returned to the desired site. This allows better control over the transfected cells and a higher level of expression can be achieved. The initial experience with gene therapy experiments using synovial cells indicates that this may become a viable option in the future.

Many other issues surrounding the clinical use of growth factors need to be resolved before their benefit can be determined on a scientific basis. Timing, dosing and type of growth factor to be used remain largely unresolved issues. Once the sequence of events relating to growth factors is known, experiments to promote healing with exogenous growth factors can be initiated. One of the major problems in studying the effects of exogenous growth factors in chronic tendon problems is the lack of a reliable animal model. Tendinopathy is difficult to

reproduce in a laboratory animal [29,30,31]. If available, the reasons for the slow or absent healing in some of these lesions could be studied and therapeutic interventions could be designed. Currently, we rely on patient material, which often does not allow the researcher to get longitudinal or control data. Consequently, we know relatively little about the pathologic stages through which these tendon progress. Treatment strategies are limited. Further research studies will have to address these issues before significant progress can be made in the use of growth factors.

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29
Optimization of Tendon Healing

Nicola Maffulli and Hans D. Moller

Tendon disorders are a major problem in both sports and occupational medicine. Tendons have the highest tensile strength of all connective tissue due to a high proportion of collagen in the fibers and their closely packed parallel arrangement in the direction of force. The individual collagen fibrils are arranged into fascicles which contain blood vessels and nerve fibers lymph. Specialized fibroblasts, tenocytes, lie within these fascicles, and exhibit high structural organization [1,2].

Tendon healing is classically considered to occur through extrinsic and intrinsic healing. The intrinsic model produces obliteration of the tendon and its tendon sheath. Healing of the defect involves an exudative and a formative phase, which are very similar to those associated with wound healing [3]. In the extrinsic healing pathway, tenocytes migrate through chemiotaxis into the defect from the ends of the tendon sheath [4]. The process can be divided into 3 phases: inflammation, repair, and organization or remodeling. In the inflammatory phase, occurring 3 to 7 days after the injury, cells migrate from the extrinsic peritendinous tissue such as the tendon sheath, periosteum, subcutaneous tissue and fascicles, as well as from the epitenon and endotenon [5]. Initially, the extrinsic response is more florid than the intrinsic one with the rapid filling of the defect with granulation tissue, tissue debris and hematoma. The migrating fibroblasts still play a phagocytic role, and are arranged in a radial fashion in relation to the direction of the fibers of the tendon [1]. Biomechanical stability is given by fibrin.

The migrated fibroblasts begin to synthesize collagen around day 5. Initially, these collagen fibers are randomly orientated. Tenocytes become the main cell type, and over the next 5 weeks collagen is synthesized. During the fourth week, a noticeable increase in proliferation of fibroblasts of intrinsic origin, mainly from the endotenon, takes place. These cells take over the main role in the healing process, and both synthesize and reabsorb collagen. The newly formed tissue starts to mature, and the collagen fibers are increasingly orientated along the direction of force through the tendon. This phase of repair continues for approximately 2 months after the initial injury. Final stability is acquired during the remodeling induced by the normal physiological use of the tendon. This allows further orientation of the fibers into the direction of force. In addition, cross linking between the collagen fibrils increases the tendon tensile strength. During the repair phase, the mechanically stronger Type I collagen is produced in preference to Type III collagen, thus slightly altering the initial ratio of these fibers to increase the strength of the repair [6].

Despite intensive remodeling over the following months, complete regeneration of the tendon is never achieved, and the tissue replacing the tendon defect remains hypercellular. The diameter of the collagen fibrils remains thinner fibrils, with reduction in the biomechanical strength of the tendon when measured per unit of cross sectional area.

In tendinopathic and ruptured Achilles tendons, there is a reduction in the proportion of Type I collagen, and a significant increase in the amount of Type III collagen [7], responsible for the reduced tensile strength of the new tissue due to a reduced number of cross links compared to Type I collagen [8]. Recurring microinjuries lead to the development of hypertrophied biologically inferior tissue replacing the intact tendon.

Cytokinetic Modulation of Tendon Healing

Growth factors and other cytokines play a key role in the embryonic differentiation of tissue and in the healing of tissues [9]. Growth factors stimulate cell proliferation and chemotaxis aid angiogenesis, influencing cell differentiation. They regulate cellular synthetic and secretory activity of components of extracellular matrix, and influence the process of soft tissue healing.

In the normal flexor tendon of the dog, the levels of basic fibroblast growth factor (bFGF) are higher than the levels of platelet derived growth factor (PDGF). In injured tendons, the converse is true [10]. Under the influence of PDGF, chemotaxis and the rate of proliferation of fibroblasts and collagen synthesis are increased [11]. Fibroblasts of the patellar tendon show increased proliferation in vitro after the administration of bFGF [12]. In addition, an angiogenic effect is evident [13]. During the embryogenesis of tendon, bone morphogenic proteins (BMP), especially BMP 12 and 13, cause increased expression of elastin and collagen Type I. Also, animal studies demonstrated that BMP 12 exerts a positive effect on the healing processes of the patellar tendon [14].

The growth factors of the transforming growth factor beta superfamily induce an increase in mRNA expression of Type I collagen and fibronectin in cell culture experiments [15].

As the high expression of collagen Type I is probably essential to achieve faster healing of tendons, there should be a shift from the initial production of collagen Type III to Type I early in the healing process. The aforementioned growth factors could potentially be used to influence the processes of regeneration of tendons therapeutically. However, it is unlikely that a single growth factor will give a positive clinically relevant result. The interaction of many factors present in the appropriate concentration at the right time for the correct duration will be necessary.

Gene Therapy to Provide Growth Factors

Growth factors have a limited biological half-life. Given the complexity of the healing process of tendons, a single application of growth factors is unlikely to be successful. As there is no bio-availability of oral proteins, repeated local injections would be necessary to maintain levels in the therapeutic range, which may prove technically difficult in operatively treated tendons. The transfer of genes for the relevant growth factors seems an elegant alternative [16]. After cellular uptake and expression of genes a high level of the mediators can be locally produced and secreted.

To achieve this goal, vectors, either viral or nonviral, would enable the uptake and expression of genes into target cells. Viral vectors are viruses deprived of their ability to replicate into which the required genetic material can be inserted. They are effective, as the introduction of their genetic material into host cells forms part of their normal life cycle. Nonviral vectors have specific characteristics which enable penetration of the nucleus, e.g. liposomal transport. The genes are released in the vicinity of the target cells without systemic dilution.

Vectors can be transferred using 2 main strategies. Using *in vivo* transfer, the vectors are applied directly to the relevant tissue. *In vitro* transfer involves removal of cells form the body, the gene transfer *in vitro* and subsequent culture of these cells before they are reintroduced into the target site. Direct transfer is less invasive and technically easier, and can be started during treatment of the acute phase of the injury. A disadvantage is the nonspecific infection of cells during the injection process. In addition, due to the amount of extracellular matrix present, a vector with high transgenic activity is necessary to be able to transfer the gene to enough cells.

Indirect transfer of genes is safer. The relevant cell type is isolated and genetically modified. Prior to reintroduction into the body, cells can be selected and tested for quality. Due to the work involved in this technique, it would be more suitable for the treatment of degenerative processes instead of the acute injuries. The first studies on the feasibility of this procedure have been conducted using marker genes [17]. The main gene used, LacZ, codes for the bacterial beta galactosidase which is not present in eukaryotic cells. The addition of a suitable substrate changes the staining properties of the cells which express the new gene, allowing to ascertain the effectiveness of transmission and the duration of expression of the foreign gene. With the vectors currently available, the gene is expressed for 6 to 8 weeks in tendon tissue [18]. Using this strategy, the transfer and expression of PDGF gene into the patellar tendon of rats lead to an increase in angiogenesis and collagen synthesis in the tendon over 4 weeks. Gene expression of this duration could influence the whole healing process of tendons and could be the start of an optimized healing process.

In summary, even successful tendon healing does not reconstitute a normal tendon, and the result is functionally satisfactory despite morphological differences and biomechanical weakness compared to a normal tendon. The therapeutic use of growth factors by gene transfer to produce a new tendon which is biologically, biomechanically, biochemically and physiologically more "normal" is promising, but still far from clinical practice.

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30
Gene Therapy in Tendon Ailments

Vladimir Martinek, Johnny Huard, and Freddie H. Fu

Introduction

The treatment of musculoskeletal disorders has improved during the last 20 years due to enormous progress in the understanding of basic biology and biomechanical principles. Based on this knowledge, new conservative methods, minimally invasive operative techniques, modern rehabilitation programs, and innovative approaches were developed and successfully applied for treatment. Despite this progress, there are still limitations in the therapy of musculoskeletal tissues with a limited healing capacity [1].

Tendon tissue has a low blood supply, cell turnover, and metabolism, similar to menisci or articular cartilage. For this reason, the healing of tendon injuries is prolonged and often results in the formation of inferior scars or remaining lesions [2]. In orthopedics, both the healing of acute tendon ruptures and degenerative changes of the tendons represent a serious problem for the clinician. New approaches have been investigated to improve the healing of tendon tissue and to develop new, biological therapies for tendon ailments [3].

Growth Factors

Growth factors, or cytokines, have been identified as substances that are capable of improving the healing process in tissues [4]. They are peptides that can be generated both by the resident cells at the injury site (e.g. fibroblasts, endothelial cells, mesenchymal stem cells) and by invading reparatory cells (e.g. macrophages, monocytes, platelets). Growth factors can stimulate cell proliferation, migration and differentiation as well as the matrix synthesis in different tissues can induce certain healing responses in the injured tissue [3]. Meanwhile, the genes encoding for these growth factors have been identified.

Growth Factor Effecting Tendon Healing In Vitro

Using recombinant DNA technology, we are now able to produce growth factors in large quantities [5]. To determine which growth factors can promote the healing of tendon tissue, the role of different cytokines has been investigated in a large number of *in vitro* experiments [3]. Despite major limitations of studying the effects of growth factors on cultured tendon cells, several cytokines have been identified as potent promoters of fibroblast or endothelial proliferation, synthesis of extracellular matrix proteins such as collagen and proteoglycans, cell migration, and differentiation (Table 30-1). From a review of the literature, the proliferation of fibroblasts is most powerfully stimulated by platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and insulin-like growth factor (IGF), while transforming growth factor β (TGFβ) and IGF-1 are capable of increasing the matrix synthesis of tendon cells [2,3]. Cytokines such as endothelial growth factor (EGF), hepatocyte growth factor (HGF), bone morphogenetic protein 2 (BMP-2), PDGF, and interleukin IL-1) also showed positive effects on fibroblast migration across collagen coated membranes [6].

Growth Factor Facilitated Tendon Healing In Vivo

Two strategies are applied for the determination of specific growth factors improving the healing of tendons and ligaments [2]. The first strategy, which involves the detection of cytokine receptors and endogenous growth factors within the tendon tissue following injury, defines specific growth factors participating in the physiological process of tendon healing. Regarding this method, immunohistochemical staining of ligament and tendon samples have shown up-regulation of PDGF, TGF-β, bFGF, and EGF by 3 to 7 days following injury [7,8]. The second strategy investigates the effect of direct growth

Table 30-1. Gene delivery vectors

Nonviral	Viral
liposomes	Adenovirus
DNA gene gun	Retrovirus
DNA-protein complexes	Adeno-associated virus
naked DNA	Herpes simplex virus

factor application in injured tendons and ligaments. Exogenous application of PDGF and bFGF at the time of injury increases the strength, stiffness, and breaking energy of healed ligaments. Basic FGF proved also to be a potent angiogenic factor [3,9–11]. However, the need for long-term release or high dosages can result in reduction of their beneficial effect, which is characteristic of the complex relationships associated with many cytokines [9,10].

Limitations of Growth Factor Application

Although the direct injection of these human recombinant proteins displays some beneficial effect on the healing process, very high dosages and repeated injections are often required due to the relatively short biological half-life [4]. Another major limitation of using these human recombinant growth factor proteins to promote healing is their delivery to the injured site [12]. In fact, the use of various strategies such as polymers, pumps, and heparin, has been investigated to achieve sustained levels of therapeutic proteins. Although these approaches have been capable of improving the local persistence of the growth factor proteins, the success remains limited. Among the different methods developed for local administration of growth factors, gene therapy based on the use of various gene transfer techniques has proven to be the most promising [13].

Gene Therapy

Definition of Gene Therapy

Gene therapy is a technique relying on the alteration of the cellular genetic information. Originally, gene therapy was conceived for the manipulation of germ-line cells for the treatment of inheritable genetic disorders, which is greatly limited by the inefficient technology and considerable ethical concerns. Meanwhile, gene manipulation of somatic cells has been widely achieved for many tissues [13]. Gene therapy can be used in orthopedic applications using the transfer of genes encoding for growth factors, cytokines, and antibiotics, for example, into the target tissue. Thus, therapeutic substances can be highly and persistently produced directly at the site of injury, with therapeutic levels of growth factors, which can improve the healing process.

Vectors

In order to achieve gene expression, the transferred DNA material has to enter the nucleus, where it either integrates into the chromosomes of the host cells or remains separated from the host DNA in the form of an episome. After transcription, the generated mRNA is transported outside the nucleus and serves as a template for the production of proteins (e.g. growth factors) by ribosomes (Figure 30-1). The cells transduced by the vector can express the growth factors and cytokines of interest and become a reservoir of secreting molecules capable of improving the healing process.

Viral and nonviral vectors can be used for delivery of genetic material into cells (Table 30-2). Nonviral gene transfer systems are usually easier to produce and have a significantly lower cell toxicity and immunogenicity than the viral vectors, but the overall use of the nonviral systems has been hindered by the low transfection efficiencies [14]. Different approaches are being investigated to improve non-viral gene transfer, e.g. the use of necrotic agents to increase the permeability of the nonviral vectors and the development of liposomes, however, their success remains limited.

Currently, viral gene vectors present the most efficient method [12]. Before using a virus for gene therapy, all genes encoding for pathogenic proteins must be deleted

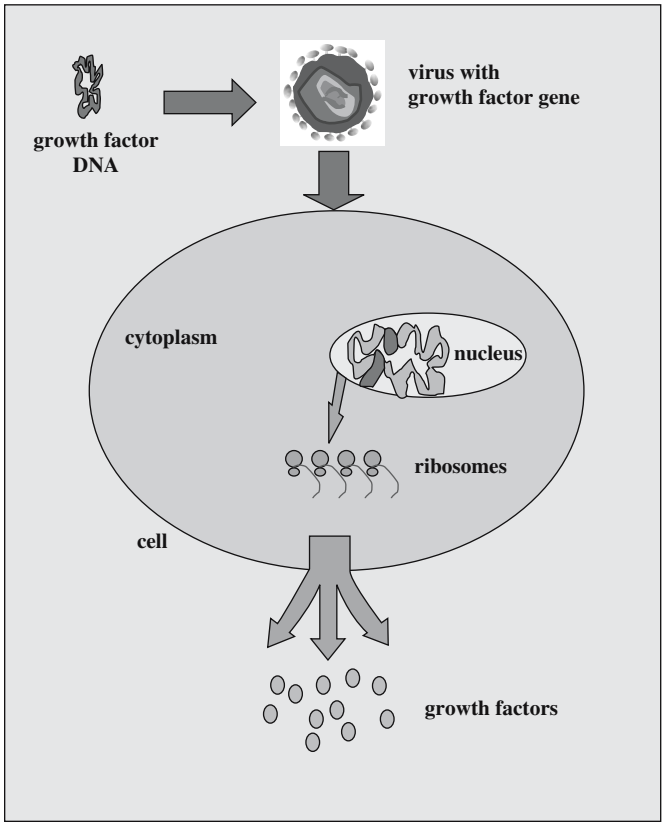

Figure 30-1. Principle of viral gene transfer.

TABLE 30-2. *In vivo* therapeutic gene therapy in tendons. Abbreviations: HVJ-hemagglutinating virus of Japan; PDGF-B-platelet derived growth factor B; HGF/SF-hepatocyte growth factor/scatter factor; BMP-2-bone morphogenetic protein 2; ODN-oligodeoxynucleotide

Author/Year	Species	Strategy	Vector	Cytokine
Nakamura, 1998 [21]	rat/patellar tendon	in-vivo	HVJ liposome	PDGF-B
Natsuume, 1998 [22]	rat/patellar tendon	in-vivo	HVJ-liposome	HGF/SF
Nakamura, 2000 [23]	rabbit/MCL	in-vivo	HVJ-liposome	Anti Decorin ODN
Martinek, 2001 [20]	rabbit/semitendinosus tendon	ex-vivo	Adenovirus	BMP-2

and replaced therapeutic gene. In fact, many years of basic research were required to characterize and remove the pathogenic genes from the viral genomes. The native ability of the virus to enter (infect) the cell and express its own genetic material within the infected cell could then be utilized. The most commonly used viruses in gene therapy currently are adenovirus, retrovirus, adeno-associated virus, and herpes simplex virus. Although viral vectors display a high efficiency of transfer to many cell types, their cytotoxicity (herpes simplex virus), immunogenicity (adenovirus), and inability to tendinosis post-mitotic cells (retrovirus) have limited their general application for gene therapy purposes. Consequently, new viral vectors with reduced cytotoxicity and immunogenicity are under development [5].

Strategies

Various gene delivery strategies such as direct and systemic delivery can be used to achieve gene transfer to the knee and the musculoskeletal system (Figure 30-2). The systemic delivery of the viral vectors consists of injecting the vector in the bloodstream, resulting in the dissemination of the vector to the target tissues. This approach represents a major advantage when the target tissue is difficult to reach by direct injection. Moreover, systemic delivery often displays better distribution of the vectors within the targeted tissues since direct injection of the vectors often results in a localized expression at the injected site. The major disadvantages of this technology are the high amount of vectors required and the lack of specificity of expression, because the majority of the vectors will be absorbed by the lung and the liver tissue. Furthermore, the low vascularity renders this approach inefficient for some musculoskeletal injuries including tendon disorders.

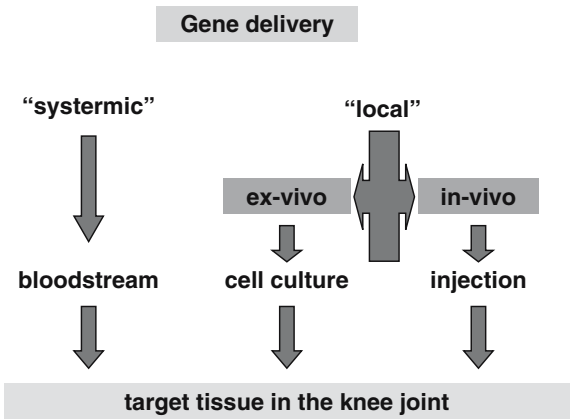

FIGURE 30-2. Gene therapy *s*trategies.

Two basic strategies for direct gene therapy to the musculoskeletal system have been extensively investigated [12]. The vectors either are directly injected in the host tissues (direct, *in vivo*), or the cells of the injured tissue are removed, genetically altered (transduced/transfected) *in vitro*, and implanted in the tissues (indirect or ex vivo). The direct, *in vivo* method is technically easier, but the *ex vivo* gene delivery offers more safety as the gene manipulation takes place under controlled conditions outside the body. Furthermore, the ex vivo approach leads to the delivery of growth factors and cytokines as well as endogenous cells capable of responding to the stimuli and participating in the healing process. Tissue engineering-based approaches which aim at using cells from different tissues (mesenchymal stem cells, muscle derived cells, dermal fibroblast) to deliver genes may give rise to further approaches for improving the healing process of various tissues of the musculoskeletal system. Selecting the appropriate procedure depends on various factors such as the division rate of the target cells, pathophysiology of the disorder, availability of cells from the injured tissues, and the type of vector used.

Gene Transfer in Tendons and Ligaments

In the last few years, several investigators have reported successful gene transfer to tendons and ligaments. A number of investigators have demonstrated the feasibility of transferring marker genes directly or indirectly to uninjured and respectively injured tendons [14–19]. Genetically modified, heterologous fibroblasts were injected into rabbit patella tendon where they migrated from the site of injection and integrated into the crimp pattern of the patellar tendon [15]. In our own study, rabbit semitendinosus tendon explants were transduced *ex vivo* with adenoviral vectors expressing various marker genes. In this experiment, the transgene lacZ

expression on the surface of the tendons in tissue culture and *in vivo* after osseous implantation of the tendons in rabbit knee joints was demonstrated up to 8 weeks following transduction [19] (see Figures 30-3 and 30-4, see color insert). In a subsequent experiment, the rabbit semitendinosus tendon explants were transduced *ex vivo* with adenoviral vectors expressing the bone morphogenetic protein 2 (BMP-2). After implantation of the transduced tendons in the bone tunnel, the tendon-bone interface showed a significantly enhanced osteogenic activity in the adjacent bone and ossifications in the implanted tendons (Figure 30-4, see color insert). This histological appearance was confirmed by significantly improved tensile properties of the implanted tendons during the biomechanical pullout testing [20]. Meanwhile, other authors also have demonstrated successfully therapeutic gene transfer to tendon tissue in animal studies [21,22] (see Table 30-3). Direct delivery of a PDGF gene and hepatocyte growth factor/scatter factor (HGF/SF) into the healing rat patellar tendon ligament led to enhanced collagen synthesis and angiogenesis [21,22]. In another approach, down-regulating of the proteoglycan decorin, a collagen fibrillogenesis inhibitor, by direct gene transfer of antisense decorin oligodeoxynucleotides using an *in vivo* method of hemagglutinating virus of Japan (HVJ) conjugated liposomes led to an increased development of larger collagen fibrils in early scar and a significant improvement in scar failure strength of medial collateral ligaments of rabbits [23].

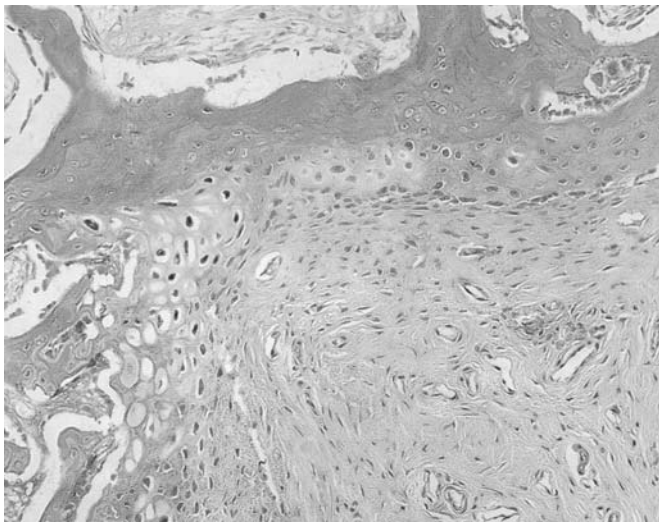

Figure 30-4. Tendon-bone interface 6 weeks after implantation of *ex-vivo* adenovirally transduced rabbit semitendinosus tendon in the osseous femoral tunnel, (H/E, 60¥). (See color insert.)

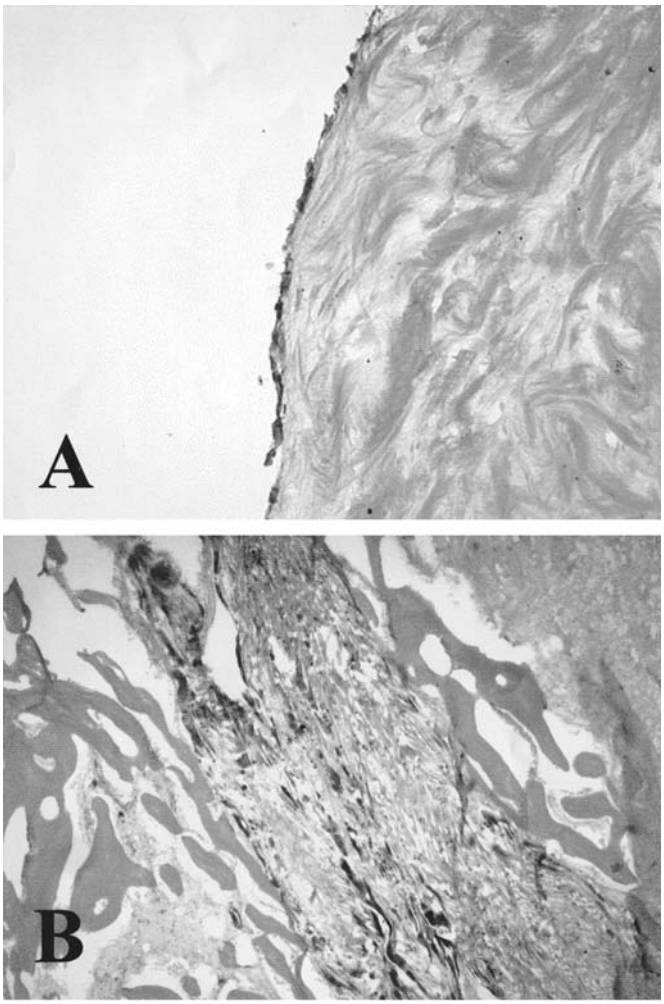

Figure 30-3. Transgene expression of lacZ on the surface of adenovirally *ex vivo* transduced rabbit semitendinosus tendon after 4 weeks in tissue culture (A) and 4 weeks following implantation in the rabbit femoral tunnel (B). (See color insert.)

Current Limitations of Gene Therapy

For the treatment of musculoskeletal disorders including tendon injuries, the major concern for the use of gene therapy is safety. While gene therapy may represent a "last chance" treatment option in cases of malignancies or severe genetic disorders (e.g. Duchenne muscular dystrophy, Gaucher disease, cystic fibrosis), the risk of many side effects and potential consequences of gene therapy may be unacceptable in elective orthopedics. Virus vectors integrating into the genome of the cells bear the danger of insertional mutagenesis [24]. Possible abnormal regulation of cell growth, toxicity due to chronic overexpression of the growth factor protein and development of a malignancy are theoretically conceivable, although cases have never been reported. Vectors that do not integrate into the native DNA avoid these risks, but remain greatly limited by the lack of persistent expressions of the desired genes in the target tissues. The loss of expression of the transferred gene over a few weeks is a frequent and not fully understood phenomenon, especially for adenoviral vectors. However, a temporary and self-limiting gene expression could be useful in the treatment of musculoskeletal injuries, for which only transient high levels of growth factors might be necessary to promote the healing response.

Gene Therapy in Treatment of Tendon Ailments

Clinically relevant issues from the field of tendon disorders for which therapeutic interventions based on gene therapy could have a significant impact are basically rotator cuff tendon tears, flexor tendon injuries, tendinopathy, and the healing of tendon grafts used for cruciate ligament reconstruction [25].

Rotator Cuff Lesions

Rotator cuff lesions represent a significant age-related clinical problem with a complex etiology and prolonged treatment course. A rotator cuff rupture is the consequence of a disturbed tendon physiology caused either by extrinsic (surrounding structures) or by intrinsic factors. Possible intrinsic factors, which are fairly difficult to influence, include decreased vascularity and hypoxia, intrinsic degeneration, and fibrocartilaginous degeneration [26]. Due to these limiting intrinsic factors, healing of the rotator cuff following injuries and after operative cuff reconstructions is limited. Introduction of therapeutic genes into a diseased or injured rotator cuff tendon to release growth factors promoting cell proliferation, matrix synthesis or ingrowth of blood vessels represent a new promising treatment alternative.

Tendon Injuries

Among tendon injuries, Achilles tendon ruptures represent a relevant clinical problem with an urgent demand for improvements and therapeutic alternatives. There is not only the difficulty of healing of the tendon proper, but there is also the problem of healing between the tendon and the tendon sheath, which can lead to adhesions and a massive loss of function [25]. In most cases, a rupture of the flexor tendon follows a process of tendon degeneration that cannot be treated sufficiently with current methods. For this reason, the main goals of gene therapy after tendon injuries is to prevent the tendon degeneration, to promote the tendon regeneration after injuries, and finally to avoid development of adhesions in the healing tendon.

Tendinopathies

Tendinopathies such as tennis and golfer's elbow or jumper's knee are very common repetitive motion symptoms with a microscopic picture of microtraumatic injury response. Apparently, these chronic conditions are caused by small tears within the tendon tissue without a true inflammatory response. The typical microscopic findings are the alteration of the size of mitochondria as well as alterations in the nuclei of the internal fibroblasts or tenocytes [27]. A local genetic modification of these cells could be helpful to stop the collagen breakdown and to maintain the regeneration of the tendon tissue. Also, the improvement of the blood supply of the involved tendon area e.g. by the transfer of the vascular endothelial growth factor (VEGF) is imaginable.

ACL Tendon Grafts

The current standard treatment for anterior cruciate ligament (ACL) or posterior cruciate (PCL) ruptures is the replacement with autologous or allogenous tendon grafts. The golden standards are the middle third of the patellar tendon with the adjacent bone blocks from the patella and the tibial tuberosity or the quadrupled semitendinosus/gracilis tendon graft [28]. After implantation the grafts undergo a process of degradation and replacement by a scarlike tissue, which is mechanically inferior in comparison to the normal ACL. For this reason, the rehabilitation after ACL reconstruction is prolonged and the return to sports delayed for at least 6 months. Gene therapy approaches could be effective in regeneration of biologic ACL auto-/allografts and in improvement of tendon-to-bone healing after usage of ACL tendon grafts. Following gene transfer of appropriate growth factors, the healing of cruciate ligament tears may become feasible and finally replace the current routine of complete ACL replacement.

Future Directions

Although gene therapy is not yet established as an approved therapeutic technique, a great potential exists for the treatment of tendon disorders in the future. Until recently, only a few effective therapeutic gene therapy techniques have been shown in humans [12]. At experimental level, many studies have been performed successfully to prove the feasibility of gene delivery into different tissues of the musculoskeletal system. Beyond this stage, initial experimental studies demonstrated positive effects of transduced genes (especially BMP-2, IGF-1, TGF-β) *in vivo*. The main obstacle today seems to be the availability of vectors carrying therapeutic genes, but great progress has been noticed in many laboratories working on the engineering of these vectors [5]. In general, gene therapy will potentially help us to develop efficient therapies for tissues with low healing capacity (cartilage, meniscus, tendons) and for other disorders such as osseous nonunion or arthritis.

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31
Tendon Regeneration Using Mesenchymal Stem Cells

Stephen Gordon, Mark Pittenger, Kevin McIntosh, Susan Peter, Michael Archambault, and Randell Young

Introduction

Mesenchymal stem cells (MSCs) have the potential to differentiate into the tenocyte lineage and regenerate diseased or injured tendons. Because there is a limited base of research on the tendon lineage, illustrative examples from the bone and cartilage lineage are included to define more clearly the clinical potential of this cell-based approach to medicine. The concluding sections of this chapter consider the emerging data that support the use of allogeneic/universal MSCs as a cost-effective and practical approach for clinical delivery of MSCs.

Defining Mesenchymal Stem Cells

The name human mesenchymal stem cell (hMSC) generally refers to culture-expanded stem cells that retain the ability to differentiate to several mesenchymal lineages. While mesenchymal stem cells are present among marrow stromal cells, not all marrow stromal cells are mesenchymal stem cells. Bone marrow stroma functions to support the hematopoietic stem cells (HSCs) that provide for erythroid, myeloid, and lymphoid cell types needed throughout life. Bone marrow is a complex tissue composed of many cell types including the hematopoietic progenitors and their progeny, mesenchymal stem cells fibroblasts, and endothelial cells, as well as osteoblasts, and adipoblasts.

Early evidence for the multipotential nature of adherent marrow-derived cells came from experiments in which animal marrow cells were cultured *in vitro*, then implanted at ectopic sites in animals. The characterization of the newly formed tissue demonstrated that the implanted cells could produce several cell types. Many investigations on the nature of adherent marrow stromal cells have been performed since Alexander Friedenstein and his colleagues first demonstrated the osteogenic potential of guinea pig bone marrrow fibroblasts in the 1960s [1,2]. Placement of the cells into diffusion chambers allowed the flow of nutrients, but not migration of host cells. The production of connective tissues following implantation verified that the differentiation capacity lay with the donor marrow cells, not the host cells. This experimental approach was extended to rabbit bone marrow cells by Maureen Owen and colleagues, who further characterized differentiation of the cells [3]. Owen also described a limited lineage diagram similar to that proposed for hematopoietic stem cells [4]. Arnold Caplan and colleagues, first working with nonhuman mammalian bone marrow-derived cells, and later isolating human MSCs [5], further developed the concept of the connective tissue mesenchymal stem cell and provided a more extensive lineage diagram, encompassing additional tissues [6]. This field has developed through the contributions of many investigators, and the reader is referred to several reviews [7–11].

Pittenger and colleagues have developed reproducible isolation methods and characterized a population of human bone marrow-derived cells that are believed to represent the mesenchymal stem cell that persists in the adult [12]. This work provides several important findings. First, these investigators improved previous isolation and culture conditions and demonstrated the homogeneous nature of the cultured cells. Second, they described *in vitro* culture conditions that reproducibly promoted differentiation exclusively to 3 desired mesenchymal lineages. Third, they demonstrated that, using human cells of clonal origin, they could recapitulate the same degree of *in vitro* differentiation as seen in the parental population, verifying that individual cells held the potential for proliferation and multilineage differentiation (see Figure 31-1, see color insert).

In Vitro Assays

In vitro assays permit an efficient and timely means to determine that MSCs are pluripotent. For example, when

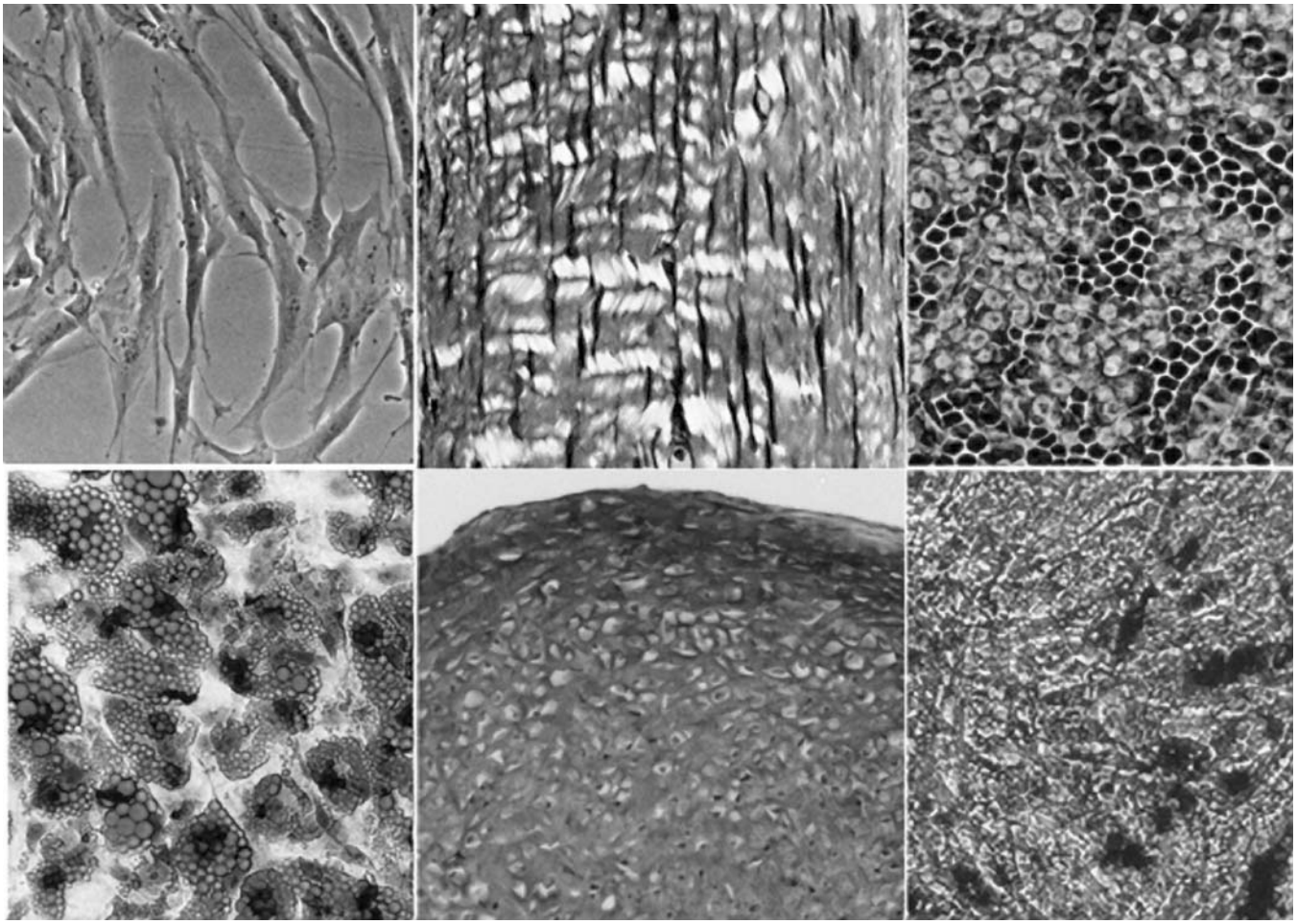

FIGURE 31-1. Multilineage potential of mesenchymal stem cells (MSCs). Upper left: Human MSCs expanded in monolayer culture. Upper middle: Rabbit MSCs differentiated *in vivo* into the tenocyte lineage. Upper right: Human MSCs provided stroma support for hematopoietic stem cells growing on a MSC monolayer. Lower left: Adipogenic *in vitro* differentiation of human MSCs with oil red O staining of lipid vacuoles. Lower middle: *In vitro* chondrogenic differentiation of human MSCs with antibody staining for Type II collagen. Lower right: *In vitro* osteogenic differentiation of human MSCs with staining for alkaline phosphatase in red and von Kossa mineral staining in dark silver. (See color insert.)

MSCs are considered for a new preclinical study or for application with a new delivery matrix, the first stage of testing would be *in vitro* assessments, assuring that these cells differentiate into the appropriate mesenchymal lineage. Additionally, *in vitro* assays allow scientists to explore the factors released by differentiating cells, factors that affect the differentiation process, and gene expression patterns during differentiation.

Osteogenic Lineage

A reproducible system for *in vitro* osteogenic differentiation was established by Jaiswal et al [13]. Optimal culturing conditions were established by testing a range of media additives and measuring the best response with assays for alkaline phosphatase, reactivity with antiosteogenic cell surface monoclonal antibodies, modulation of osteocalcin mRNA production, and the formation of mineralized extracellular matrix. hMSCs derived from second or third passage and cultured in DMEM base media containing 100 nM dexamethasone, 0.05 mM L-ascorbic acid-2-phosphate, and 10 mM β-glycerophosphate produced optimal results. Figure 31-1 (lower right) shows the osteogenic lineage.

Chondrogenic Lineage

Chondrogenesis has been induced by culturing hMSCs in micropellets in a serum-free DMEM with a supplement that included 100 nM dexamethosone, 10 ng/ml transforming growth factor-β3, and other agents [14]. High-glucose DMEM yielded significantly larger pellets than low-glucose DMEM. Within 14 days, differentiated hMSCs secreted an extracellular matrix containing Type

II collagen, aggrecan, and proteoglycans. No significant amounts of Type I collagen were observed. Figure 31-1 (lower middle) shows the chondrogenic lineage.

Tenocyte Lineage

In vitro tenogenesis was accomplished by means of a construct that consisted of a pretensioned, polyglyconate suture to which cultured MSCs were affixed by way of their contraction of a Type I collagen gel around the suture [15]. This assay was performed in a glass trough culture device in which the pretensioning was provided by a bow-spring formed from stainless steel surgical Kirschner wire (0.89 mm diameter) with a mean restoring force of 4.9 ± 0.7 N on the suture. When the MSC-matrix constructs were observed grossly after 40 hours of incubation in the culture device, the matrix had been contracted to approximately 30% of the original diameter. Histological examination of constructs demonstrated an organized structure of elongated cells aligned with the matrix in the direction of tensile load along the longitudinal axis. Figure 31-1 (upper middle) shows the MSC tendon construct after it had been implanted at a repair site. Studies on the effect of initial cell-seeding density [16] indicated that constructs seeded at 4 and 8 million cells/mL, as compared to 1 million cells/mL, were more contracted, with greater cell orientation and elongation.

A comparative study of constant versus cyclic tension in the *in vitro* tenogenesis model was performed by Archambault et al [17]. The constant, static tension was produced by a bowspring formed from Kirschner wire, and the cyclic tension was provided via glass fiber filter tabs on each end of the glass trough loaded onto a Bio-Stretch device. The cyclic loading conditions were 10% longitudinal strain for 5 seconds at 0.1 Hz for 30 minutes followed by a rest period of 90 minutes and repeated continually for 15 days. Two proteins found in developing tendons, Type VI and Type XIV collagen (undulin), were measured in these *in vitro* models. Type VI collagen increases occurred about 2 days earlier with cyclic versus static load. Type XIV collagen was present in increased amounts over time for cyclic loading and not present with static loading. Collagen synthesis with cyclic loading was twice the level of synthesis measured for static loading as measured by ^{3}H L-proline incorporation. Figure 31-2 demonstrates histological photomicrographs for *in vitro* tenogenesis with constant and cyclic loading. Overall, this *in vitro* system was a good model to demonstrate cellular function and changes in matrix organization in MSC-mediated tenogenesis.

Another *in vitro* tenogenesis study was designed to investigate the expression of the transcriptional activation genes Eyes Absent 1 and 2 (Eya1 and Eya2) in hMSC-based tendon constructs. The Eya genes are

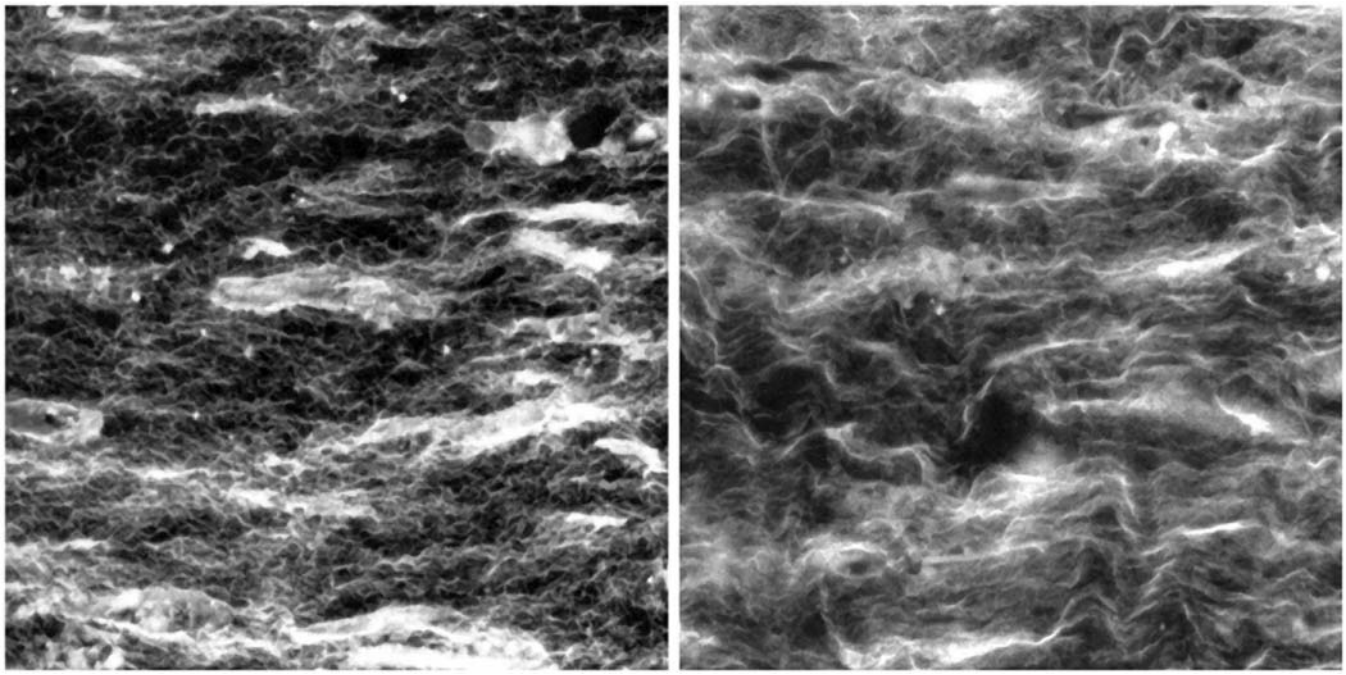

FIGURE 31-2. Histology of *in vitro* tenogenesis of mesenchymal stem cells at 48 hours with constant and cyclic loading. Photomicrographs of H&E stained paraffin sections viewed with fluorescent light at 600x magnification. Photo on left showed some longitudinal organization of a static loaded MSC construct. Photo on right showed a crimp pattern, similar to neotendons in fetal tissue samples, with a cyclic loaded MSC construct.

turned on early and transiently in developing mammalian embryonic limbs [18,19]. Static tensioned constructs showed increasing levels of Eya1 and unchanging Eya2 with time. In comparison, cyclic tensioned constructs showed downregulation of both Eya1 and Eya2. These results suggested that *in vitro* tenogenesis of hMSCs may follow a patterning program similar to fetal development, and analysis of homeobox gene expressions may help to understand this process.

In Vivo Studies with MSCs to Repair Injured Tendons

A 1-cm-long gap injury model in the rabbit Achilles was used to compare a suture alone versus a cell-collagen gel composite contracted onto a pretensioned suture [15]. The cell-composite was formed with autologous MSCs in the same manner as described in the static *in vitro* tendon studies above. The repair was evaluated at 4, 8, and 12 weeks following surgery. Both structural and material properties of the cell-treated implants were typically about twice the value of controls at all time points. Importantly, the rate of increasing properties with time was greater in the cell-treated implants. Table 31-1 displays material property values at three time points. Qualitative histological examination showed that cell-treated repairs were larger in cross section and better organized than suture alone natural repair tissue.

Another rabbit model was repair of the central third of the patellar tendon, which is a clinical situation arising when using this tissue as a donor graft for anterior cruciate ligament (ACL) reconstruction. Again, the autologous MSC-composite structure was prepared as described above and evaluated at 3 different seeding densities. The control repair was an unrepaired defect without a suture strut. MSC-treated repair tissues were, on average, significantly stronger and stiffer than natural repair at 12 and 26 weeks postsurgery. No statistically significant differences were observed among the three seeding densities tested.

Allogeneic/Universal MSCs

Initial preclinical studies using MSCs to treat musculoskeletal disorders focused on autologous cells that required a delay between the harvest, isolation, and expansion of MSCs and the implantation for repair and regeneration of damaged tissues. In some clinical situations such as degenerative disorders and injuries requiring several weeks of stabilization, autologous MSC therapy would be feasible. Even in these cases, the cost of delivering such a product would be high, due to labor-intensive handling and culture of each individual patient sample and costly release and safety testing.

An improved product configuration would be the use of allogeneic or universal MSCs. Some advantages of an allogeneic MSC product would include: no initial MSC harvest procedure, no delay in applying the treatment, easier tissue handling requirements, no risk of tumor cell contamination from patients with musculoskeletal tumors, low cost of release testing, low final cost of treatment, and availability off-the-shelf. McIntosh et al. [20] have determined that hMSCs appear to be nonimmunogeneic; therefore, allogeneic MSC therapy is the current focus of preclinical studies (Figure 31-3, see color insert).

TABLE 31-1. Material properties for treated (T) and control (C) repairs of the Achilles tendon in a rabbit model

Material properties	Normal (N = 5)	Repair	4 wk N = 13	8 wk N = 13	12 wk N = 12
Modulus (MPa)	337.5 ± 205.8	T	53.4 ± 4.9	90.3 ± 10.4	114.4 ± 7.6
		C	33.5 ± 7.0	62.2 ± 9.2	67.9 ± 9.8
Stress-maximum	41.6 ± 18.9	T	8.6 ± 0.8	10.5 ± 1.4	15.5 ± 1.1
($N \cdot mm/mm^3$)		C	4.7 ± 1.1	7.2 ± 1.3	8.0 ± 1.2
Strain energy density-maximum	3.9 ± 0.4	T	1.0 ± 0.1	0.8 ± 0.2	1.4 ± 0.2
($N \cdot mm/mm^3$)		C	0.4 ± 0.1	0.5 ± 0.1	0.6 ± 0.1
Strain energy density-failure	6.7 ± 3.6	T	1.3 ± 0.1	1.2 ± 0.2	2.1 ± 0.4
($N \cdot mm/mm^3$)		C	0.7 ± 0.1	0.9 ± 0.1	1.0 ± 0.1

Material properties (mean + SEM) were compared for normal, treated (suture plus MSC construct) repair, and control (suture only) repair of a 1 cm gap in the rabbit gastrocnemius tendon. Modulus represented the increase in stress for an incremental increase in strain in the linear region of the curve; stress-maximum was the largest stress developed during failure testing; strain energy density-maximum was the area under the stress-strain curve to maximum stress; strain energy density-failure was the area under the stress-strain curve to complete loading. All treated means were significantly greater than controls ($p < 0.05$) except for the strain energy density values at 8 weeks.

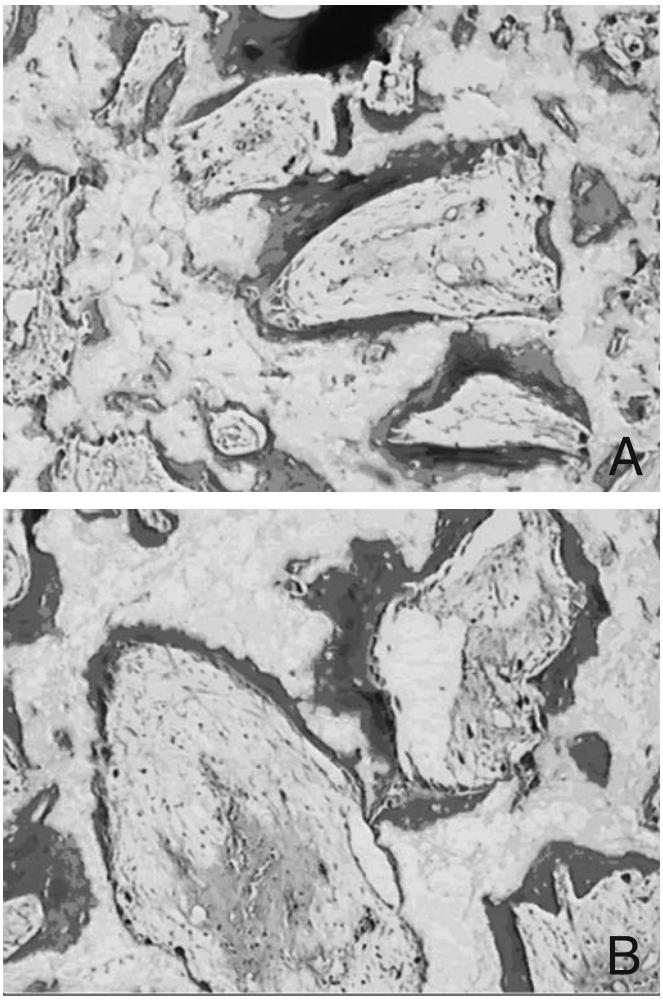

FIGURE 31-3. Histological comparison of allogeneic and autologous MSC bone regeneration. Histological sections from subcutaneous canine study. Samples harvested at 6 weeks, processed through standard decalcified paraffin histology, and stained with modified aniline blue. Off-white color indicated remaining matrix. Blue/brown color indicated new bone formation. Vascular ingrowth was also evident. The images represented allogeneic (A) and autologous (B) MSC implants. (See color insert.)

In Vitro Evidence Supporting Allogeneic MSCs

The primary *in vitro* assay to assess the immunologic activity induced by MSCs was the mixed lymphocyte reaction (MLR). This assay is performed by mixing peripheral blood mononuclear cells (PBMCs) from one individual with the PBMCs from a different individual. A subset of T cells in each PBMC population recognize allogeneic major histocompatibility antigens (Class I and Class II) on cells of the other population and respond by proliferation, which is measured by the uptake of ^{3}H-thymidine. The assay can be performed as a "one-way" MLR in which one of the PBMC populations is inactivated by irradiation or chemicals to prevent it from proliferating. Thus, the one-way MLR can be used to assess the responsiveness of a recipient against potential donors.

The one-way MLR has been used to determine the immunogenicity of allogeneic MSCs. Purified T cells cultured with allogeneic irradiated PBMCs proliferated vigorously, whereas T cells cultured with MSCs (from the same PBMC donor) did not proliferate [20]. Pretreatment of the MSCs with IFNγ, which is known to upregulate MHC Class I and Class II alloantigens on the MSCs, did not result in a response to the MSCs. The experiment was repeated using MSCs that were differentiated in the osteoblastic lineage as stimulator cells in the MLR. Again, there was no proliferative T cell response, indicating that immune privilege was preserved in the bone lineage [20].

In vitro tenogenesis studies of Class I and Class II histocompatibility antigens were performed using antibody staining. Class I staining was observed in monolayer MSC and tenogenic cultures, while Class II staining was not positive in either culture condition. This demonstrated that the immunogenic potential of MSCs is not changed upon tenogenic differentiation.

In Vivo Evidence of Benefits for Allogeneic MSCs

Several studies have been conducted to determine that implanted allogeneic MSCs do not induce an immunologic response and have the capacity to regenerate the appropriate tissue in vivo. The studies described here have used canine and baboon models to demonstrate allogeneic bone formation.

The initial step in studying allogeneic MSC implantation in canines was to prove that the donor-host relationship is immunologically mismatched. Purchasing animals from different vendors in geographically distinct regions was the initial procedure. The canines were then evaluated for satellite markers of dog leukocyte antigen (DLA), which is analogous to human HLA testing. Polymerase chain reaction (PCR) identifies specific sequences of the key chromosomal segments of class I and class II antigens as clusters of similar and dissimilar histocompatibility complexes. These results allow interpretation of matched and unmatched pairs of donor and host [21,22]. Finally, the MLR techniques described above can be used to confirm an immunologic mismatch between animals. T cell proliferation of recipient PBMCs cultured with inactivated donor PBMCs, a one-way MLR, indicates that the animals are histocompatibility mismatched [20]. In the two canine experiments described below, all three conditions were positive, demonstrating that the canines were completely mismatched, allogeneic donor/host pairs.

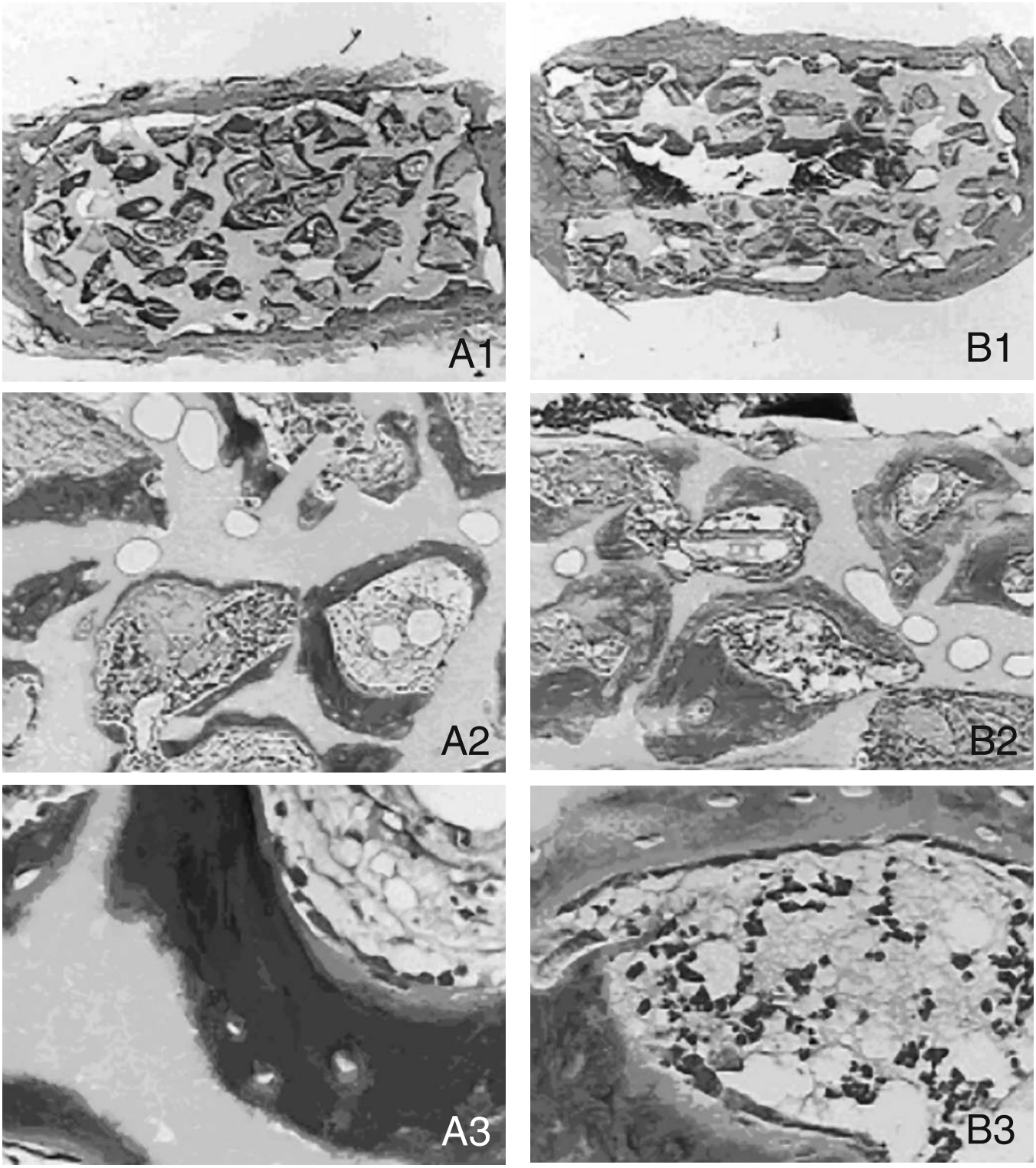

FIGURE 31-4. (A) Bone formation in autologous MSC-loaded HA/TCP cylinders harvested 10 weeks post-implantation in subcutaneous tissue (MAB stain, Magnification 8×, 16×, & 40×). Slides stained with modified aniline blue, wherein the orange coloration indicated mature bone and the bright blue staining showed new osteoid. The light blue areas were remaining ceramic matrix. (B) Bone formation in allogeneic MSC-loaded HA/TCP cylinders harvested 10 weeks postimplantation in subcutaneous tissue (MAB stain, Magnification 8×, 16×, & 40×). Slides stained with modified aniline blue, wherein the orange coloration indicated mature bone and the bright blue staining showed new osteoid. The light blue areas were remaining ceramic matrix. (See color insert.)

In one study [23], a total of 14 canines received subcutaneous implants containing allogeneic canine MSCs (cMSCs). Implants were surgically inserted bilaterally with unmatched, allogeneic donors in one limb and autologous cMSCs, from an earlier harvest from the same animal, in the contralateral limb. The implants consisted of cMSCs loaded onto porous hydroxyapatite/tri-calcium phosphate (HA/TCP) cylinders (3 mm O.D. × 6 mm long). Each limb received 3 implants. Histologic scoring of the explanted cubes, read in a blinded manner, demonstrated that 12 of 14 canines receiving allogeneic implants were positive for cartilage and/or bone at 6 weeks postimplantation. Similarly, autologous implants had 12 of 14 positive results, indicating no difference in bone tissue formation potential between the allogeneic and autologous MSCs. Histologic and antibody staining for macrophage and monocyte markers demonstrated minimal cell infiltration, equivalent to that of native tissue. Figure 31-3 shows examples of *in vivo* histologic comparisons between autologous and allogeneic MSC implants. In addition, absence of CD3 staining verified the lack of T cell infiltration into the MSC-ceramic implant. Overall, there was no observed immunologic response to the allogenic MSCs.

A pilot study in baboons was conducted to evaluate allogeneic bone formation in a subcutaneous site. HA/TCP ceramic cylinders, 6 mm in length and 3 mm in diameter with a central canal, were loaded with either autologous or allogeneic MSCs. The allogeneic MSCs came from donors with complete HLA mismatches in both Class I and II alleles. Cylinders were incubated for 10 hours to allow MSC attachment, and then held at room temperature for 36 hours prior to implantation. After 10 weeks, the cubes were explanted and processed for histological analysis. Figure 31-4 (see color insert) shows autologous and allogeneic paraffin histologic sections at three magnifications. All cylinders showed extensive bone formation, whether they contained MSCs from an allogeneic donor or isolated from the animal's own marrow. No inflammatory response or rejection of the implants was noted.

Another study [24,25] evaluated the ability of allogeneic canine MSCs to heal a critical-sized 21 mm, osteoperiosteal, segmental defect in the canine femur. The bone was stabilized with a fixation plate, and the cMSCs were loaded onto an appropriately sized HA/TCP matrix. Healing response was evaluated at 4, 8, and 16 weeks with an N = 4 at each time point. Bone was present in the bone-implant interface as early as 4 weeks following surgery. At 8 weeks, a large bony callus was observed. At 16 weeks, there was a substantial amount of bone formation. These results were compared to a previous study [26], using the same surgical model, that compared empty defects to cell-free and cMSC loaded HA/TCP matrices. The amount of bone formation with allogeneic MSCs was similar to that observed in the autologous case, both of which were greater than for implants with no MSCs added. In all cases with allogeneic MSCs there was no histological evidence of an immunologic response by the host.

Clinical Applications and Future Directions

Current tendon regeneration studies using MSCs are encouraging. However, additional preclinical research is required before clinical applications can be considered. Clinical applications for tendon could include: Achilles injuries requiring surgery and long rehabilitation; flexor tendon injuries of the finger, which heal poorly with adhesions and reduced range of motion; and mid-third patellar tendon harvests for ACL reconstruction, which heal slowly and incompletely with long-term donor site morbidity.

Ligament injuries, such as a torn ACL, are a major clinical challenge that could be significantly improved with a regenerative treatment approach. Recent studies in a normal and OA goat knees have indicated that MSCs can survive and remain attached to soft tissues in the harsh environment of an inflamed knee joint. Therefore, research has been initiated into regeneration of ACLs. Research and development will progress sequentially from autologous to universal MSC-based therapy for ligament regeneration.

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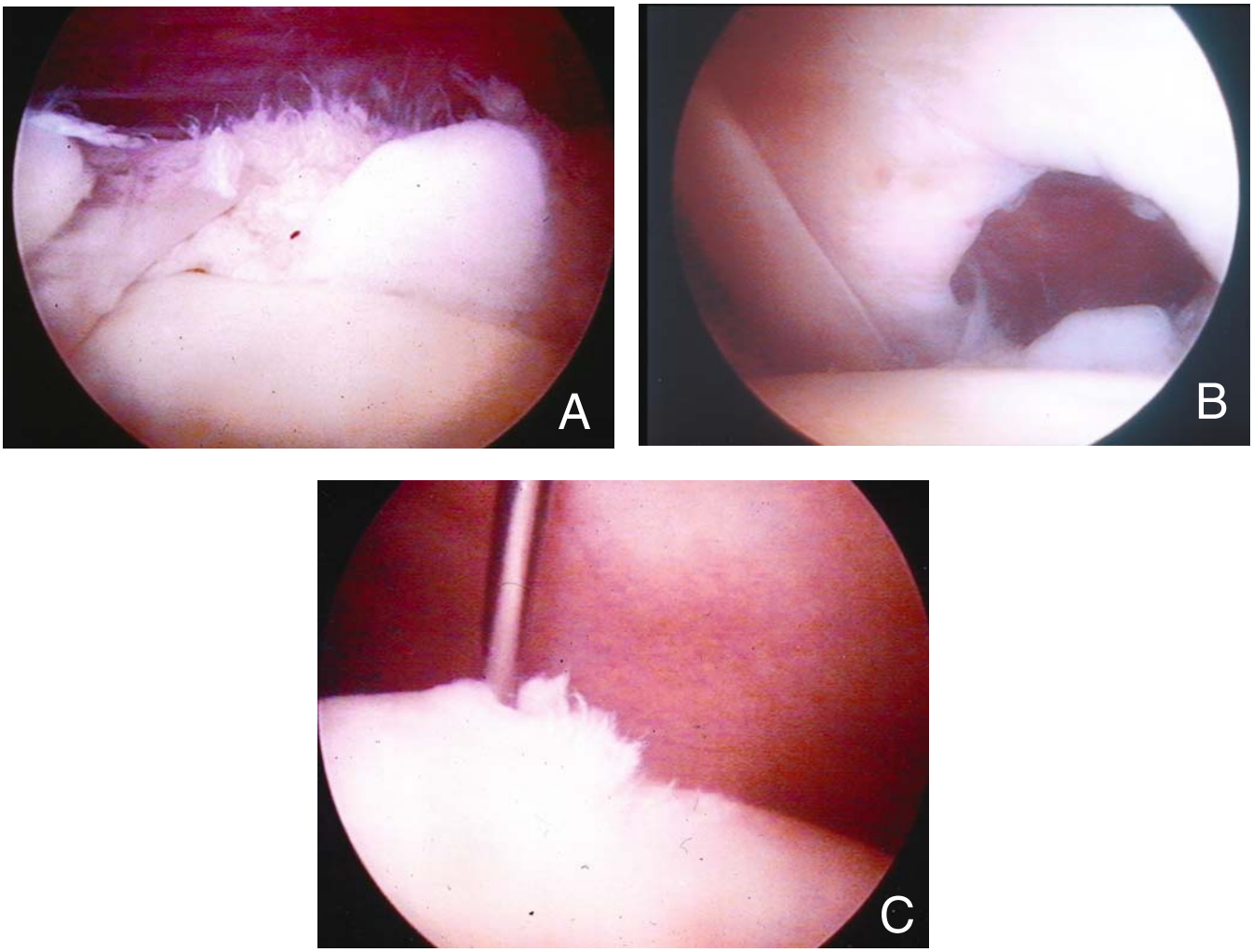


Figure 12-9. Arthroscopic appearances. (A) Bursal side full-thickness tear. (B) Joint side full-thickness tear. (C) Bursal side partial-thickness tear.

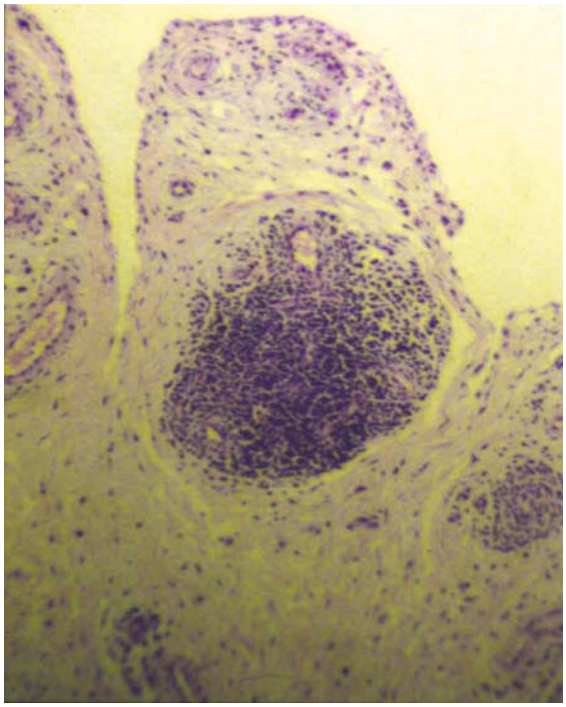


Figure 19-2. Histological appearance of tibialis posterior tendon with villi and follicula.

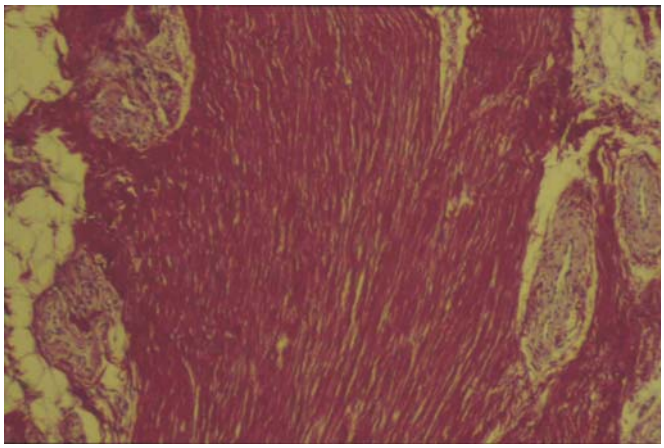
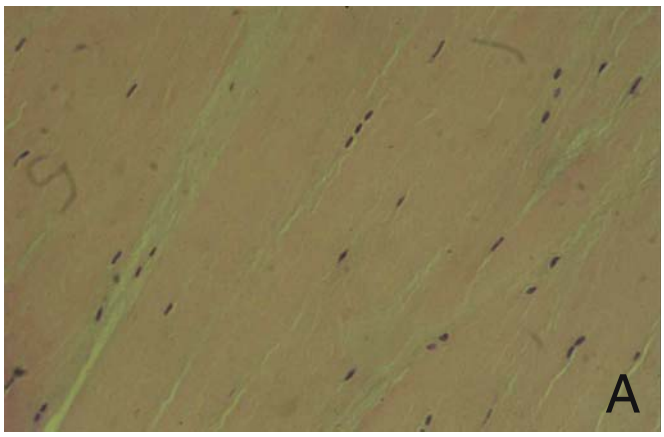
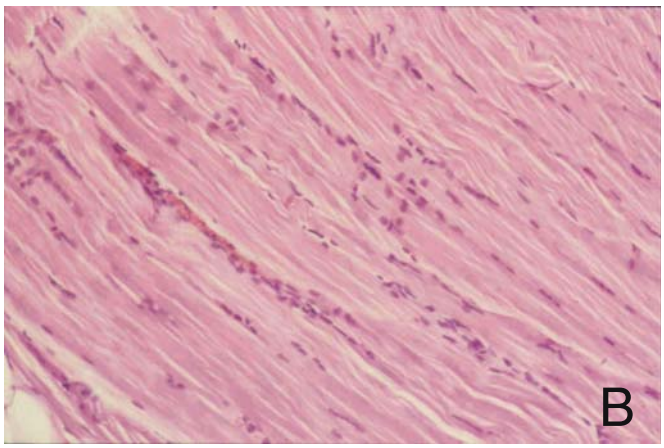


Figure 19-3. The tendinous tissue of tibialis posterior is surrounded by areolar tissue and many newly formed capillaries.





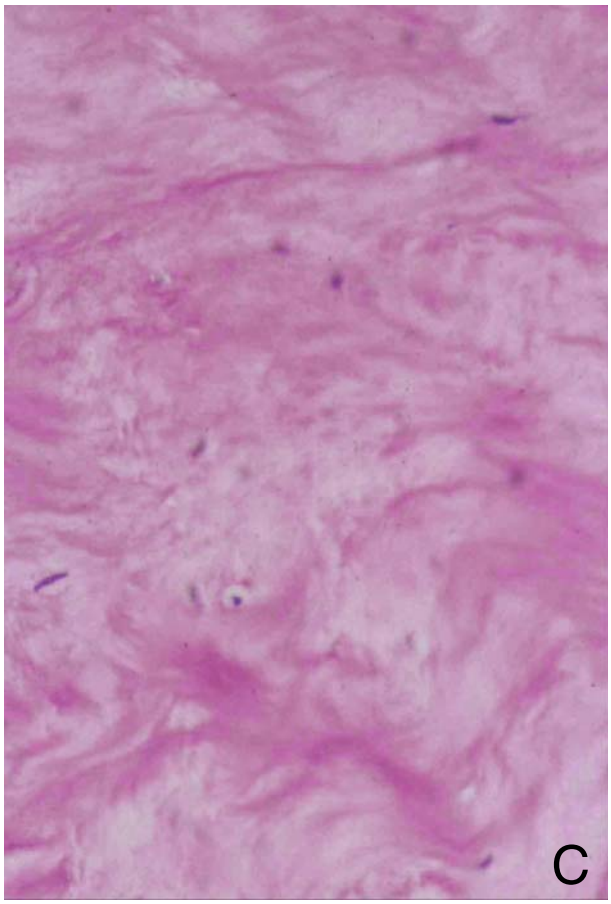


Figure 19-4. Normal tendon with scattererd elongated cells (A), slightly pathologic tendinous tissue (B) with islands of high cellularity and initial disorganization, and highly degenerated tendon with some chondroid cells (C).

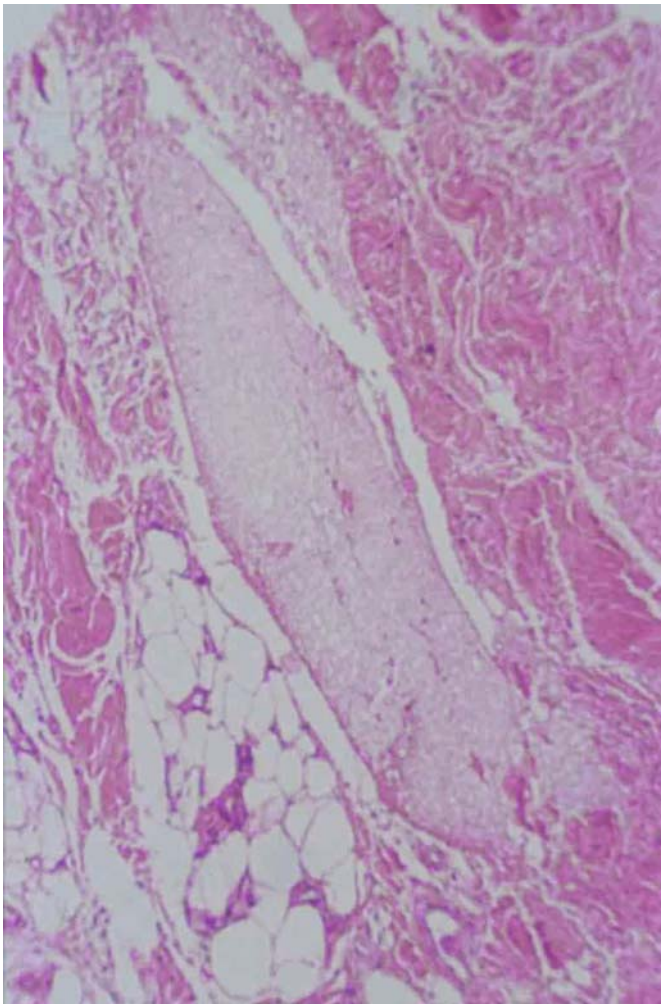


Figure 19-5. Effects of corticosteroids injection: a crystal is surrounded by amorphous and alveolar tissue and the fibrillar organisation is no-longer recognized.

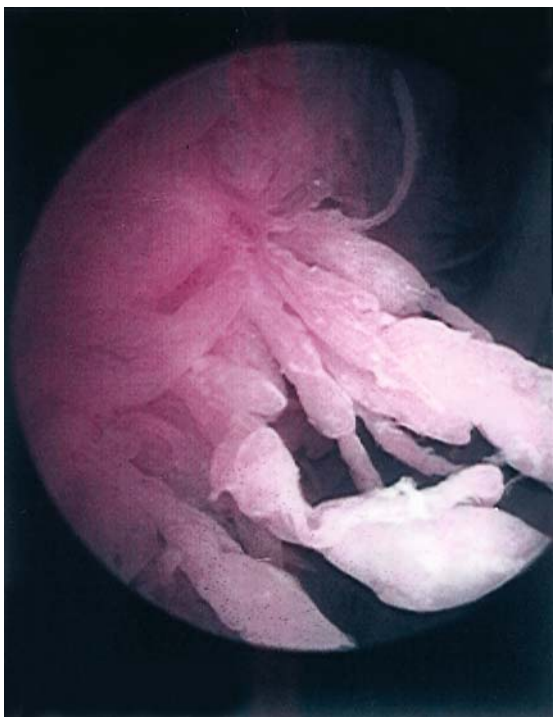


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FIGURE 22-4. A, Hypertrophic synovitis (arthroscopic view). High levels of prostaglandins make this tissue prime target for anti-inflammatory therapy.

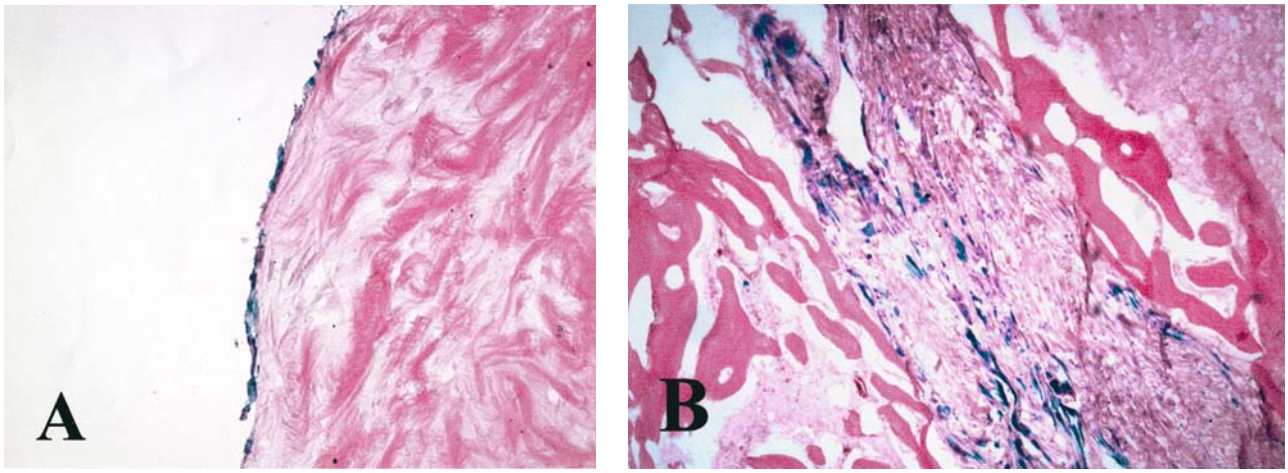

FIGURE 30-3. Transgene expression of lacZ on the surface of adenovirally *ex vivo* transduced rabbit semitendinosus tendon after 4 weeks in tissue culture (A) and 4 weeks following implantation in the rabbit femoral tunnel (B).

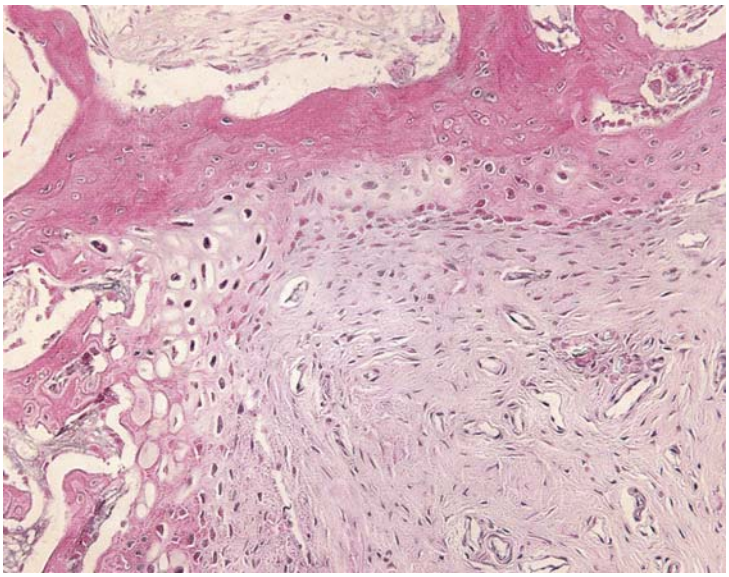

Figure 30-4. Tendon-bone interface 6 weeks after implantation of ex-vivo adenovirally transduced rabbit semitendinosus tendon in the osseous femoral tunnel. (H/E, 60¥)

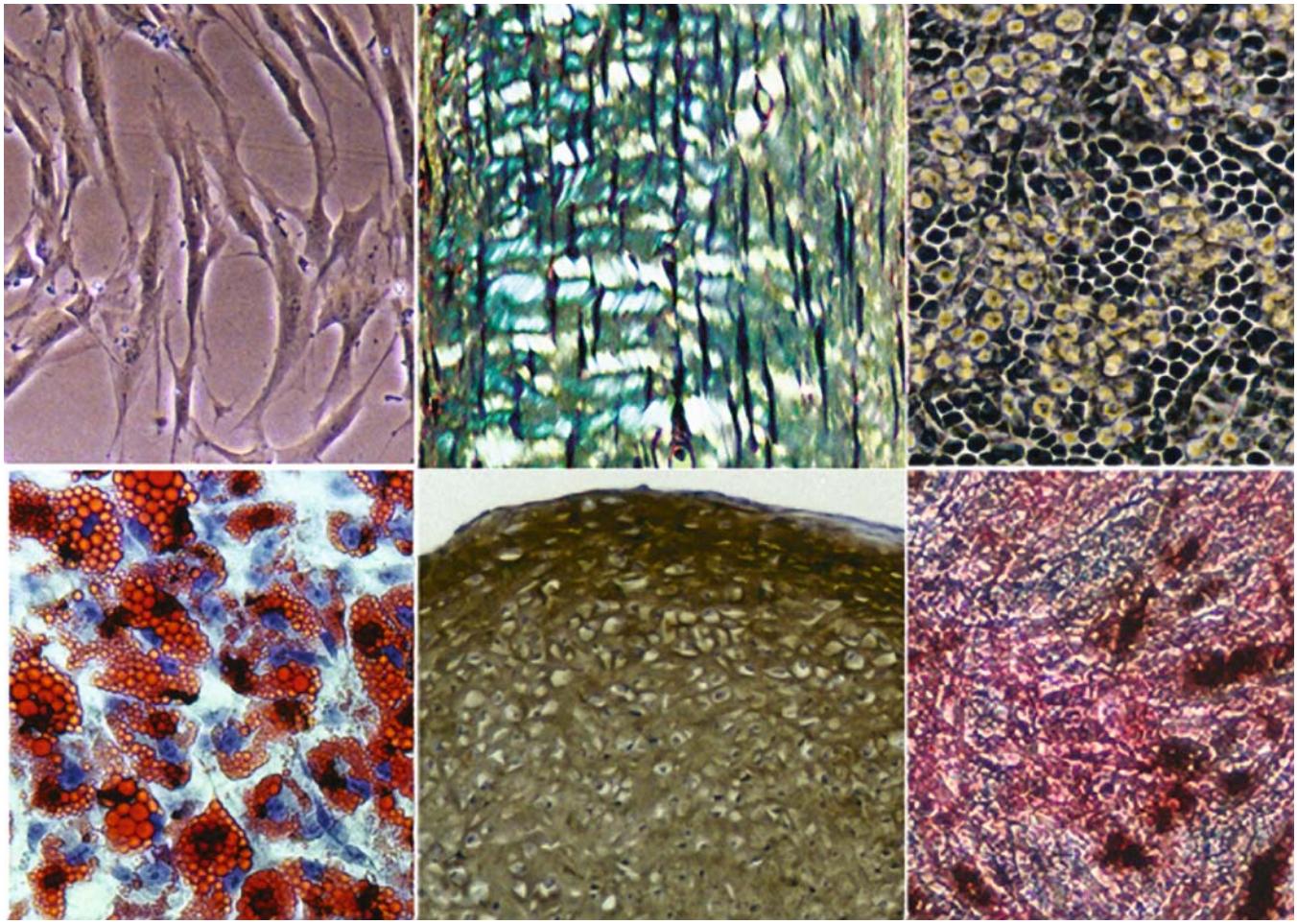

FIGURE 31-1. Multilineage potential of mesenchymal stem cells (MSCs). Upper left: Human MSCs expanded in monolayer culture. Upper middle: Rabbit MSCs differentiated *in vivo* into the tenocyte lineage. Upper right: Human MSCs provided stroma support for hematopoietic stem cells growing on a MSC monolayer. Lower left: Adipogenic *in vitro* differentiation of human MSCs with oil red O staining of lipid vacuoles. Lower middle: *In vitro* chondrogenic differentiation of human MSCs with antibody staining for Type II collagen. Lower right: *In vitro* osteogenic differentiation of human MSCs with staining for alkaline phosphatase in red and von Kossa mineral staining in dark silver.

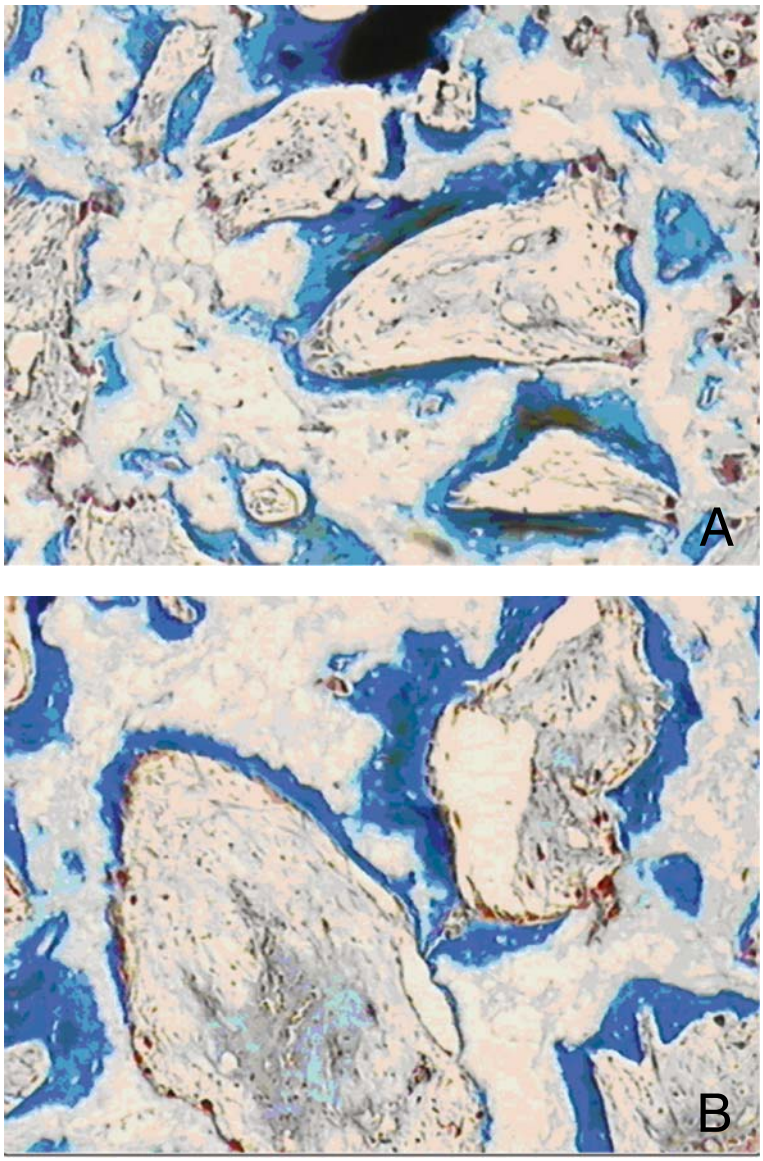

FIGURE 31-3. Histological comparison of allogeneic and autologous MSC bone regeneration. Histological sections from subcutaneous canine study. Samples harvested at 6 weeks, processed through standard decalcified paraffin histology, and stained with modified aniline blue. Off-white color indicated remaining matrix. Blue/brown color indicated new bone formation. Vascular ingrowth was also evident. The images represented allogeneic (A) and autologous (B) MSC implants.

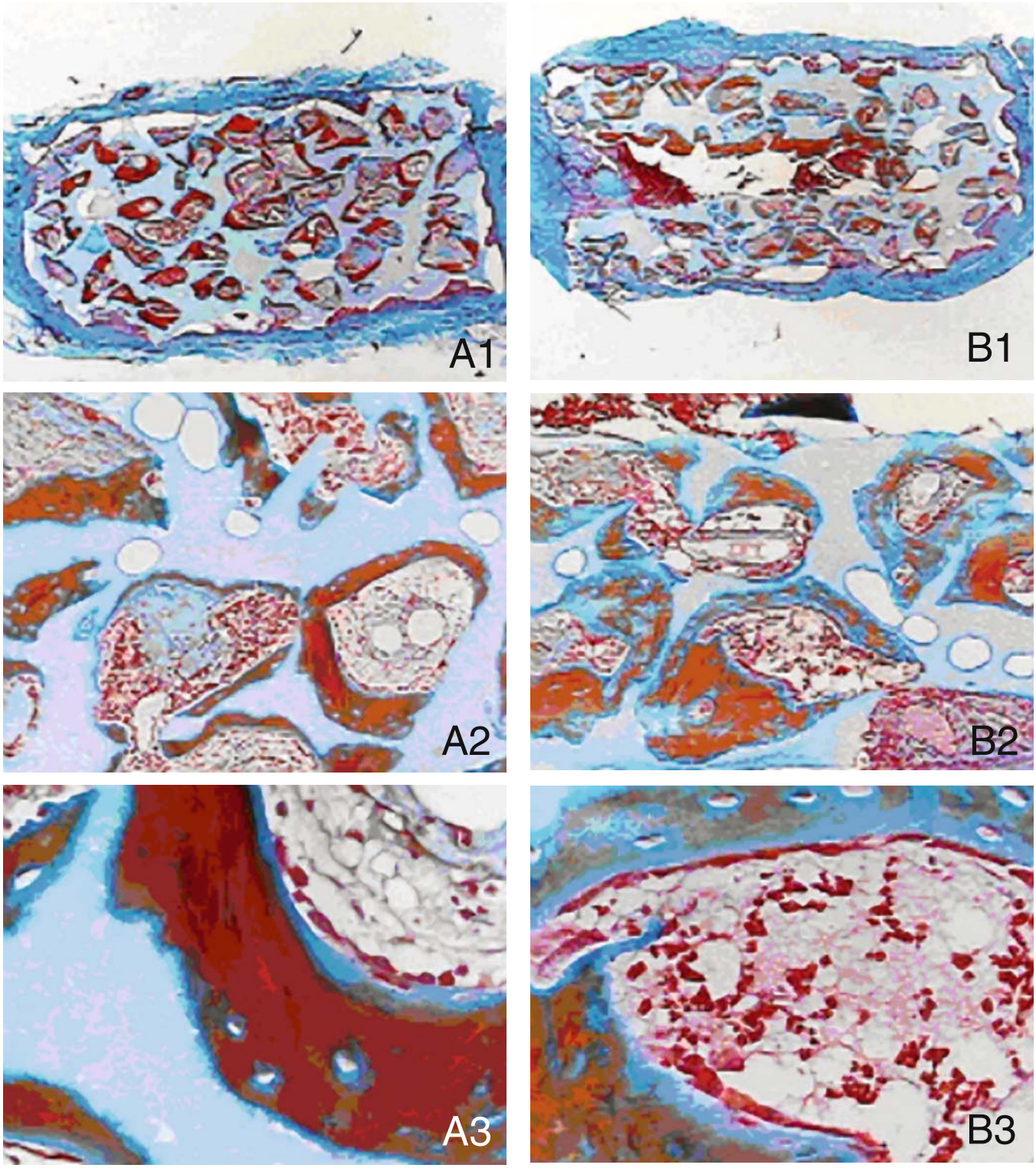

FIGURE 31-4. (A) Bone formation in autologous MSC-loaded HA/TCP cylinders harvested 10 weeks post-implantation in subcutaneous tissue (MAB stain, Magnification 8×, 16×, & 40×). Slides stained with modified aniline blue, wherein the orange coloration indicated mature bone and the bright blue staining showed new osteoid. The light blue areas were remaining ceramic matrix. (B) Bone formation in allogeneic MSC-loaded HA/TCP cylinders harvested 10 weeks postimplantation in subcutaneous tissue (MAB stain, Magnification 8×, 16×, & 40×). Slides stained with modified aniline blue, wherein the orange coloration indicated mature bone and the bright blue staining showed new osteoid. The light blue areas were remaining ceramic matrix.