

## ***Invited Review***

# **Tendons and ligaments - an overview**

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**Summary.** The structure, range of functions, blood supply, nerve supply, biochemical composition and development of tendons and ligaments are reviewed. The importance of their cells is often overlooked because of the obvious role of the extracellular matrix (ECM) in determining the physical properties of tendons and ligaments. However, it is emphasised that tendon and ligament cells have elaborate cell processes that form a three dimensional network extending throughout the extracellular matrix. The cells communicate with each other via gap junctions that could form the basis of an important load sensing system allowing the tendon to modify its ECM. Tendons and ligaments have three specialised regions along their length - the myotendinous junction, the region where tendons change direction by wrapping around bony pulleys and the enthesis (bony insertion site). The myotendinous junction is a common site of muscle strains and pulls, the wrap-around region is frequently fibrocartilaginous and a common site for degenerative change, and the enthesis may be fibrous or fibrocartilaginous according to location, and is a common site for degenerative changes or 'enthesopathies'. Enthesis fibrocartilage is just one of a series of protective devices reducing wear and tear at insertion sites. Consideration is also given to the structure and function of tendon sheaths and to the dramatic effects of exercise and deprivation on tendons and ligaments - exercise strengthens, but even relatively short periods of immobilisation can dramatically weaken tendons and ligaments.

**Key words:** Tendons, Ligaments, Entheses

### **Introduction**

Tendons and ligaments are pieces of dense connective tissue that are dominated by collagen fibres that give them a high tensile strength. The most obvious role of tendons is to transmit the pull of muscles to bones. However, not all muscles have tendons and the ones that

do are those that shorten by angulating bones at a joint (Jones, 1941). A muscle like quadratus femoris simply pulls the femur towards the ischial tuberosity with no change in angle - and has no tendon. Other aspects of tendon function are often forgotten but have been clearly stated by Jones (1941). A single tendon (e.g. the Achilles) can focus the action of several muscles onto one bone, and conversely a single muscle (e.g. tibialis posterior) can spread its action through several tendons that attach to different bones. By virtue of its tendon, a muscle can lie a great distance away from where it acts - e.g. the muscles that give bulk to the forearm but act on the fingers. It seems a general rule that muscles with long tendons pass through regions where space is at a premium - notably at the wrist and ankle (Ker et al., 1988). Thus, the carpal tunnel can accommodate many tendons simultaneously but could not cope with an equivalent number of muscles. Muscle bellies cannot tolerate pressure against ligament or bone and it is thus tendons that allow them to change direction - e.g. at the ankle malleoli.

A tendon does not act independently of its muscle, but is part of an integrated muscle-tendon unit (Trestik and Lieber, 1993; Loren and Lieber, 1995). The interactions between a muscle and its tendon convey unique properties on the unit that are difficult to predict from a knowledge of either component alone. Tendons have an important, but limited, ability to stretch - i.e. they are compliant. At first sight, their compliance is surprising, for it is obvious that tendons must be relatively inextensible in order to ensure that the force generated by a muscle is used to move a bone and not to stretch a tendon. Indeed it has been argued that it is because tendons can stretch, explains why they are so thick (Ker et al., 1988). Thicker tendons stretch less and if tendon thickness is optimised, the combined mass of the muscle-tendon unit can be minimised. Tendon compliance influences the relationship of muscles to tendons in a number of subtle ways. Importantly, it allows them to act as energy stores in locomotion - by stretching and then recoiling, less energy is needed for movement. Tendons can store 400-1800 times more elastic strain energy per unit mass than muscle (Alexander and Bennet-Clark, 1977). Fukashiro et al. (1995) have calculated that 23%, 17% and 34%

respectively of the total work performed by the calf muscles is stored in the Achilles tendon during squat jumps, counter movement jumps and hopping respectively. Different tendons can stretch to different extents. The tendon of flexor carpi ulnaris lengthens by 3.7%, but that of extensor carpi radialis longus only lengthens by 1.8% when both are loaded to maximum tension (Loren and Lieber, 1995). Work on the rabbit Achilles tendon suggests that it is highly compliant as the elongation to failure is approximately 16% (Nakagawa et al., 1996). Despite pronounced regional variations in the structure of the frog Achilles tendon (parts of the tendon contain hyaline-cell cartilage or chondroid tissue), strain is relatively constant along its length (Trestik and Lieber, 1993). Thus some tendons can regulate their mechanical properties independent of local structural differences to maintain a constant strain.

Tendons can replace ligaments in reinforcing the capsule of synovial joints e.g. the extensor tendons on the dorsal aspect of the proximal interphalangeal joints of the fingers (Benjamin et al., 1993). One of the consequences is that the tendon provides an articular surface for the head of the proximal phalanx when the finger is flexed. This is reflected by the presence of an articular fibrocartilage on the deep surface of the tendon.

Ligaments are capsular if they are local thickenings of the joint capsule or accessory if they stand clear of the joint inside or outside the capsule (Williams et al., 1995). Their principal function is to prevent excessive or abnormal movements from occurring in joints, but they also maintain the stability of joints by their proprioceptive function (see below). In addition, some ligaments extend the surface provided by bones for the attachment of muscles (e.g. the interosseous ligament of the leg and forearm), prevent tendons from bowstringing (e.g. the flexor retinaculum of the wrist) and are modified as articular discs (e.g. the triangular disc of the wrist joint).

## Structure

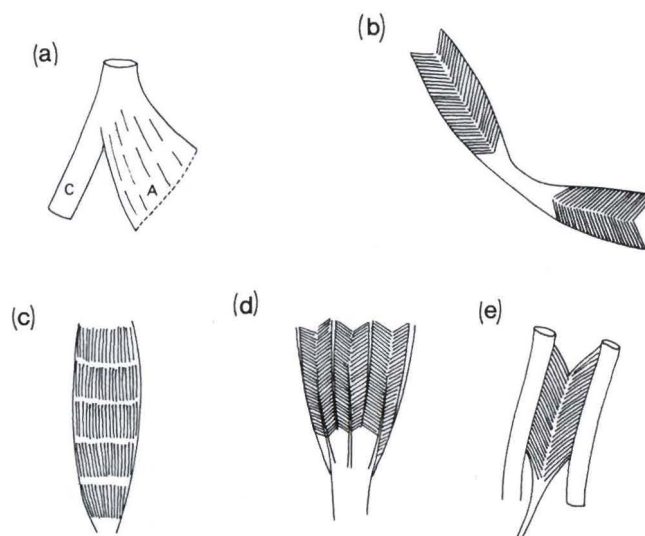
### Gross

Tendons and ligaments vary greatly in shape and length (Fig. 1). They can be long, rounded cords or short, flattened bands (called 'aponeuroses') and the cross sectional area of the more rounded tendons is usually proportional to the maximal isometric muscle force (Cook and McDonagh, 1996). Although tendons are generally found at the ends of muscles, they can also link two muscle bellies together (e.g. in digastric or omohyoid) or form tendinous areas within the muscle bellies themselves (e.g. in soleus, gastrocnemius and rectus abdominis). If a muscle has a long tendon at one end, it usually has a short tendon or aponeurosis at the other - though occasional muscles have lengthy tendons at both ends (e.g. biceps brachii). In pennate muscles, tendons extend into the muscle bellies and the muscle fibres meet them at an angle. The arrangement allows

more fibres to be packed into a muscle so that its strength is increased at the expense of its range of movement (Williams et al., 1995). Occasionally, tendons can give rise to muscles rather than originate from them - e.g. the lumbrical muscles which arise from the deep flexor tendons of the digits. The precise part of a bone to which a tendon attaches is of obvious importance to muscle action and as a general rule, tendons are attached immediately distal to the joint on which they principally act. This maximises speed of muscle action - but at the expense of mechanical advantage.

### Histological

The terms used for describing the structure of tendons and ligaments are inconsistent and based on a limited number of studies. We have stated our preferred terminology previously (Benjamin and Ralphs, 1995) and only a brief summary is given here. Collagen fibrils visible ultrastructurally are grouped into fibres that can be seen by light microscopy. In turn, the fibres are collected into fibre bundles and the bundles into fascicles. Collections of fascicles form the whole tendon or ligament and are wrapped up in a surface connective tissue layer called the epitenon or epiligament (Chowdhury et al., 1991). The fibre bundles and fascicles are enclosed in endotenon which allows them to slide relative to one another and which contributes to overall flexibility. Most human tendons are multi-fascicular and the fascicles frequently spiral along their length. This occurs in the Achilles tendon, patellar tendon and the flexor tendons of the fingers (Barfred, 1973; Semple, 1980; Amiel et al., 1995). Barfred (1973) has suggested that the sawing action of one fascicle on



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**Fig. 1.** Variations in the gross anatomy of tendons. Tendons can (a) be rounded cords (C) or flattened bands called aponeuroses (A); (b) link adjacent muscle bellies together; (c) form tendinous intersections within a muscle; (d) extend into a multipennate muscle; and (e) give attachment to muscle bellies as well as arise from them.



another may contribute to the frequency with which injuries are encountered in the Achilles tendon. He points out that spiralling of the fibres is most obvious in the region where ruptures are most common.

A striking feature of both tendons and ligaments is 'crimp' - a regular sinusoidal wave pattern of collagen fibres seen in longitudinal section. It is commonly suggested that crimp provides a buffer allowing tendons or ligaments to elongate without becoming damaged (review by Amiel et al., 1995). Irreversible damage is believed to occur only when the normal limits of crimp are exceeded.

#### *Tendon and ligament cells*

The majority of cells in tendons and ligaments are fibroblasts, although fibrocartilage cells are present at attachment sites and where tendons wrap around bony pulleys (see below). Mast cells, endothelial cells and axons are known to be present as well (review by Hart et al., 1995) and myofibroblasts appear at sites of ligament healing (Faryniarz et al., 1996).

Tendon/ligament cells have attracted relatively little interest because attention has focussed on the collagen that accounts for the mechanical properties of tendons and ligaments. However, McNeilly et al. (1996) have shown that tendon fibroblasts have an elaborate shape. They lie in longitudinal rows and have numerous sheet-like cell processes that extend into the extracellular matrix (ECM). The processes surround bundles of collagen fibres and come into contact with processes from cells in adjacent rows. These results have recently been confirmed for ligaments (Benjamin and Ralphs, unpublished observations). Both cells within the same row and those in adjacent rows are linked to each other by gap junctions that immunolabel for connexins 32 and 43 (Fig. 2). Connexin 43 occurs both where cell processes meet and between cell bodies, but connexin 32 is restricted to the junctions between cell bodies. It seems therefore as if the cells form a 3D communicating network that extends throughout the tendon/ligament and could form the basis of an important load-sensing system that allows a tendon or ligament to modulate the composition of its ECM in response to changes in loading pattern.

#### **Biochemical composition**

70-80% of the dry weight of tendons and ligaments is collagen. This is considered to be relatively inert metabolically with a half life of 300-500 days (Neuberger and Slack, 1953). Most is type I collagen, the principal tensile-resistant fibre, but smaller quantities of types III, V and VI are also present (Waggett et al., 1996). All collagen fibrils in a tendon and other connective tissues are likely to be heteropolymers and it is known for example that types I and V codistribute (Birk et al., 1990). Other heteropolymers can be formed by the association of a fibril-forming collagen (i.e.

collagen types I, II, III, V and XI) with a fibril-associated collagen (i.e. types IX, XII and XIV collagens) or with a proteoglycan (e.g. decorin and lumican). The heterotypic nature of collagen fibrils has an important bearing on the control of fibril diameter and the rate of fibril formation (Birk et al., 1990). Where and when the mixing of components begins is unclear, but it is likely to commence within the tendon or ligament cells themselves.

Water accounts for 65-75% of tendon wet weight and much of this is probably associated with proteoglycans (PGs) in the ECM (Akeson et al., 1984). Together, water and PGs have important lubricating and spacing roles in tendons and ligaments that allow collagen fibres to glide over each other (Amiel et al., 1995). The principal PGs in the tensional region of tendons are small, non-aggregating, leucine-rich PGs. They include decorin and lumican, both of which are widespread in connective tissues and believed to be important in controlling fibrillogenesis (Roughley and Lee, 1994). Recently, Campbell et al. (1996) have identified a large, aggregating PG in the collateral ligaments of the bovine knee joint that resembles versican.

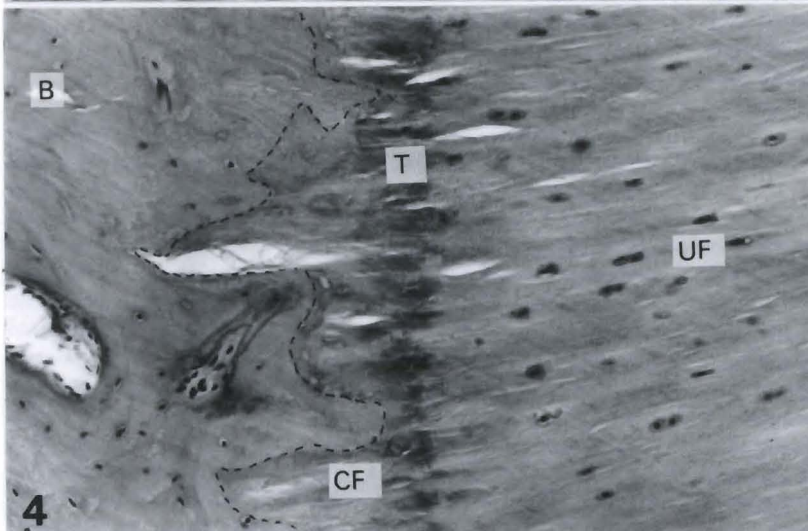
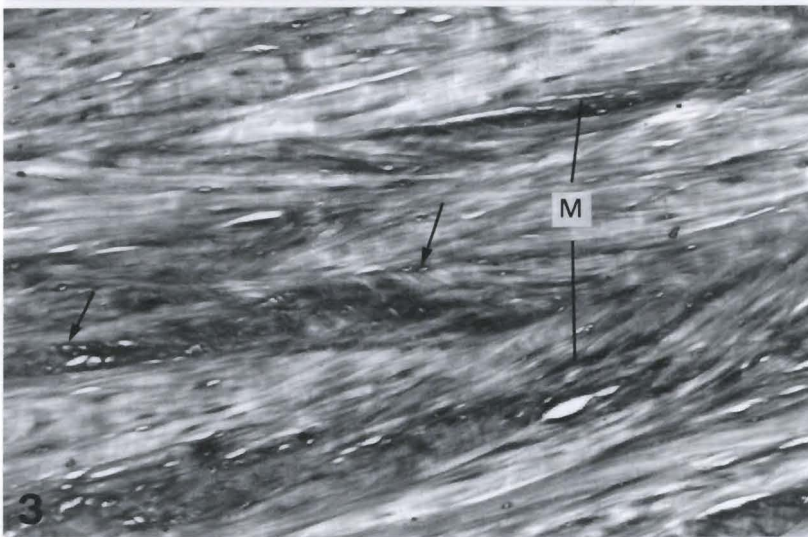
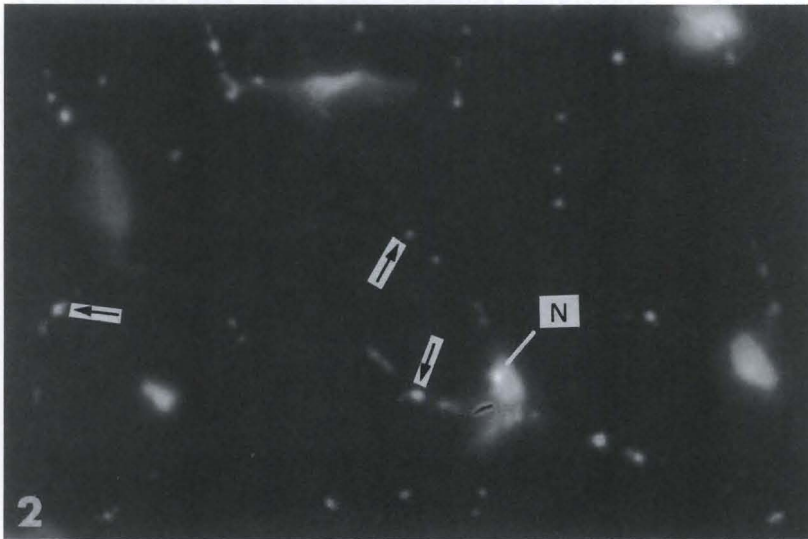
Tendons are not of uniform composition along their length. There are regional variations in water, collagen and GAG content that are likely to be reflected in biomechanical differences as well (Merrilees and Flint, 1980). Where tendons wrap around bony pulleys, they may contain type II collagen (the typical collagen of cartilage) or its mRNA (Benjamin and Ralphs, 1995; Vogel, 1995) and their GAG content is considerably higher (e.g. by a factor of 10 in the human tibialis posterior tendon; Vogel, 1995). Much of the GAG is chondroitin sulphate associated with aggrecan (Vogel et al., 1994). This is a large aggregating PG that allows articular cartilage to withstand compression and accounts for the stiffness of tendons in their wrap-around regions. The principal small PG in wrap-around tendons is biglycan but its function is unclear (Vogel, 1995).

#### **Blood and nerve supply**

##### *Blood supply*

In comparison with other tissues associated with synovial joints, tendons and ligaments have a poor blood supply. It is much less than that of muscle, synovium or bone, but is still important for normal function and for promoting healing. Blood flow is approximately 0.10 ml/g/min in rabbit tendons compared with 0.27 ml/g/min for muscle (White et al., 1964) and the total area of the ECM occupied by vessels in the medial collateral ligament (MCL) is only 1.5% (Bray et al., 1996). Blood supply increases in ligaments and tendons with exercise and during healing (Backman et al., 1991; Bray, 1995) and there is some evidence to suggest that the blood flow in ligaments decreases with tension (Dunlap et al., 1989). Maekawa et al. (1996) have made the interesting suggestion that capillaries growing into a cut anterior





**Fig. 2.** A transverse section of a deep flexor tendon from a rat hind foot showing immunofluorescence labelling for connexin 43 - a gap junction protein. The section has been counterstained with propidium iodide to highlight the position of the nuclei (N). Bright foci of immunolabel are present between the lateral cell processes of adjacent fibroblasts (arrows).

**Fig. 3.** The tendon of peroneus longus in the groove of the cuboid is highly fibrocartilaginous. Its cells are large and rounded (arrows) and its ECM is intensely metachromatic (M). Its bundles of collagen fibres interweave in various directions and this helps to prevent the tendon from splaying apart under compression.

**Fig. 4.** The fibrocartilaginous enthesis of the supraspinatus tendon in man. A zone of uncalcified fibrocartilage (UF) at the distal end of the tendon is separated from a thin layer of calcified fibrocartilage (CF) by a basophilic tidemark (T). Note that the tidemark is straight (hence the smooth marking left on a macerated bone), but that the osteochondral junction is highly irregular (broken line).



cruciate ligament (ACL) from the neighbouring infrapatellar fat pad, incorporate synovial B cells among the endothelium. Within the cut region, the B cells subsequently transform into fibroblasts that synthesise types I and III collagens.

Blood vessels in tendons have been demonstrated in a number of vascular injection studies (e.g. Kolts et al., 1994). They form a conspicuous network in the epitenon from which longitudinal vessels run in the endotenon. Arteries supplying the tendon may come from the muscle through the myotendinous junction, the bone at the insertion site and the paratenon or synovial sheath along the length of the tendon. However, where fibrocartilage is present at a tendon-bone junction, the tendon receives no blood supply from the bone as the fibrocartilage is avascular (Cooper and Misol, 1970; Benjamin et al., 1986). Particularly long tendons are supplied by a number of vessels at different points along their length (Hergenroeder et al., 1982; Zbrodowski et al., 1982; Kolts et al., 1994). Because of the longitudinal excursion that such tendons have to make within their sheaths their blood vessels must be long and coiled. The flexor tendons of the fingers for example glide about 6 cm proximally and distally in the palm during flexion and extension of the finger (Semple, 1980). Not all parts of a tendon have a blood supply and regions subject to friction, compression or torsion are often avascular (e.g. Lundborg et al., 1977; Hergenroeder et al., 1982; Kolts et al., 1994). Such areas are especially prone to tearing and calcification but the reason for this is unclear.

Less is known about the blood supply of ligaments and we know most about that of the major ligaments of the knee (Bray et al., 1990; Bray, 1995). As in tendons, vessels are most conspicuous on the surface where they form an anastomotic network in the epiligament. A much smaller number of vessels are present inside ligaments, where they run parallel to the collagen fibres and have occasional cross connections with adjacent vessels. As in tendons, there are avascular regions - e.g. the central region of the ACL (Wallace and Amiel, 1991).

#### *Innervation*

Tendons can have a rich nerve supply and needle stimulation or saline injection is known to cause pain (Canoso, 1981). In general, tendons are supplied by nerves innervating the associated muscles as well as by local cutaneous and other nerves. Typically, the receptors lie near the myotendinous and bone-tendon junctions. Encapsulated nerve endings - Golgi organs and Pacinian corpuscles, are typical of myotendinous junctions and naked nerve terminals of bone-tendon interfaces (Canoso, 1981). The Golgi tendon organs monitor increases in muscle tension and the Pacinian corpuscles monitor pressure. This in turn depends on the force of contraction. The naked nerve terminals near the bone-tendon junction act as pain receptors.

Ligaments are also well innervated and it is suggested that both encapsulated and free sensory nerve endings in the cruciate ligaments play an important proprioceptive role that contributes to the functional stability of the knee joint (Johansson et al., 1991). It is proposed that stimulation of mechanoreceptors in the ligaments influences the activity of muscle spindles around the knee. This in turn triggers the contraction of muscles that prevents the cruciate ligaments from being further stretched. Nerves are also well documented in spinal ligaments where they are implicated in back pain (Rhalmi et al., 1993).

As both nerves and blood vessels are particularly prominent on the outer surfaces of tendons and ligaments, nerves may have an important role in tissue vasoregulation (Bray, 1995; Hart et al., 1995). Nerve fibres identified in the epiligament of the rabbit MCL contain the neurotransmitters substance P and CGRP (calcitonin-gene related peptide) and are found near mast cells (Hart et al., 1995). It is possible that substance P could degranulate mast cells and thus release a panel of active substances that could amplify neural activity by their effects on ligament blood vessels and fibroblasts.

The tendon of peroneus longus in the groove of the cuboid is highly fibrocartilaginous. Its cells are large and rounded (arrows) and its ECM is intensely metachromatic (M). Its bundles of collagen fibres interweave in various directions and this helps to prevent the tendon from splaying apart under compression.

#### *Tendon sheaths*

Certain tendons, notably those in the hand and foot, are surrounded by synovial sheaths that allow them to glide freely and produce synovial fluid that contributes to their nutrition. Some tendons that lack true synovial sheaths (e.g. the Achilles tendon) have a false sheath or paratenon that develops simply as a membranous thickening of the surrounding connective tissue. True synovial sheaths resemble the synovium of joints in their structure, the peritoneum of the gut in their relationships. Thus, the tendon itself is surrounded by a visceral synovial sheath (equivalent to the visceral peritoneum) which is linked to an outer parietal layer by a mesotenon. This conveys blood vessels, lymphatics and nerves to and from the tendon. In tendons around the ankle, there is a continuous mesotenon linking the two layers of the tendon sheath, but in the flexor tendons of the fingers and toes this is reduced to a number of triangular bands or threads called vinculi (Canoso, 1981; Williams et al., 1995). In the digital flexor tendons at least, synovial diffusion provides a more important source of nutrients than vascular perfusion (Manske and Lesker, 1983a). The flexor tendons receive 90% of their nutrition by diffusion, but the corresponding extensor tendons only get 58% of their nutrients from this source - the rest comes from blood vessels (Manske and Lesker, 1983b). Mixing of synovial fluid is promoted by the bulging of synovial pockets near the interphalangeal



joints during finger flexion (Mester et al., 1995).

It is well known that synovial sheaths provides the necessary lubrication for the free excursion of tendons and that injuries lead to adhesions. The mechanism of lubrication differs fundamentally from that of synovial joints (Brand et al., 1987). Boundary lubrication occurs in tendons, but most synovial joints are lubricated hydrodynamically as one articular surface rolls over another. The difference could be significant in relation to tendon overuse injuries, because friction that occurs as a result of repetitive sliding of a tendon in its sheath may lead to tenosynovitis (Brand et al., 1987). It is generally presumed that lubrication is provided by hyaluronan in the synovial fluid. However, Banes et al. (1995) have made the intriguing suggestion that lipids in the epitenon may also be important. It is interesting that cyclic mechanical loading of tendon cells in vitro significantly increases phospholipid secretion (Brigman et al., 1994).

### Specialised regions of tendons and ligaments

#### *Myotendinous junctions*

The myotendinous junction is where force is transferred from muscle to tendon and where new sarcomeres are added during muscle growth (Garrett and Tidball, 1988; Noonan and Garrett, 1992). Its formation depends on interactions between cells of different embryological origins. The myoblasts that give rise to limb muscles are derived from the somites, whereas connective tissue cells in the tendon and muscle come from somatopleural cells. Thus, a coordinated interaction must occur between cells of different origins for a myotendinous junction to form. The junctions show striking adaptations for force transfer (Garrett and Tidball, 1988). Extensive infoldings of the muscle cell membrane significantly increase the surface area for tendon contact and reduce stress concentration. In addition, actin filaments cross link and attach to the cell membrane so as to allow force to be transmitted to the ECM. The degree of infolding is greater in slow than in fast twitch muscle fibres (Tidball and Daniel, 1986), but the contact area of both with tendon fibres is dramatically reduced after limb immobilisation (Kannus et al., 1996). This suggests that the tensile strength of the myotendinous junction is reduced by immobilisation and that this predisposes it to injury. Progressively increasing levels of exercise during the recovery period probably reduce the chances of re-injury (Kvist et al., 1995).

#### *Wrap-around regions*

In several regions of the body, notably the hand and foot, tendons can change direction one or more times before reaching their final destination. They do this by wrapping around bony pulleys such as the malleoli or passing beneath fibrous retaining straps like the extensor retinacula of the ankle. Ligaments too can bend around bone e.g. the annular ligament that holds the head of the

radius in place or the transverse ligament of the atlas that presses against the posterior surface of the dens (Williams et al. 1995). One pulley alone does not increase the mechanical advantage of a tendon, but gives it a more favourable angle of approach. Some tendons pass around a whole succession of pulleys - e.g. peroneus longus and this has profound implications for muscle action. When a tendon wraps around a pulley, it is subject to a compressive force that is roughly twice the tension generated in the tendon multiplied by half the sine of the angle through which it changes its direction (An et al., 1995). Thus a flexor tendon in the finger crossing the palmar aspect of the proximal interphalangeal joint could experience a compressive force that is 1.7 times the tension in the tendon when the finger is bent through 90°.

Tendons that change their direction of pull are frequently fibrocartilaginous, though there are significant regional differences (Benjamin et al., 1995). The most fibrocartilaginous tendons are those that wrap around bony pulleys in the foot and ankle (e.g. peroneus longus). Where the tendon of peroneus longus grooves the undersurface of the cuboid, it has a highly metachromatic ECM and collagen fibres that are arranged in a basketweave fashion around large fibrocartilage cells (Fig. 3). The interweaving of its fibres probably prevents the tendon from splaying apart under compression. In the cuboid region of peroneus longus, fibrocartilage cells are characteristic both of the tendon itself and of its endotenon and epitenon. However, in other sites, the fibrocartilage can be restricted to the endotenon or epitenon alone (Benjamin et al., 1995). Where fibrocartilage is conspicuous in tendons or ligaments, cartilage or fibrocartilage is also present on their complimentary bony pulleys. Here, the thickened and fibrocartilaginous periosteum prevents the tendon from sawing through the bone (Benjamin et al., 1995). It seems that fibrocartilage in both locations is a highly dynamic tissue. When wrap-around tendons are re-routed experimentally so that the direction of the compressive forces is altered, the tendons modulate their structure in accordance with the new load (Gillard et al., 1979; Malaviya et al., 1996). Furthermore, contact between a tendon and its bony pulley must be maintained for periosteal fibrocartilage to be present. When the long head of biceps tendon is ruptured within the bicipital groove, the fibrocartilage disappears from the bone surface (Benjamin et al., 1992).

Wrap-around tendons are frequently hypovascular (see above) and are subject to considerable wear and tear, notably fragmentation and delamination of the tendon surface (Benjamin et al., 1995). There are a number of clinical conditions affecting tendons in the region of bony or fibrous pulleys e.g. posterior tibial tendinitis and de Quervain's disease. Whether there is a causal relationship between the lack of blood vessels and the vulnerability to damage is doubtful. However, it seems reasonable to suggest that the difficulty of repairing tendons in this region is related to their poor blood



supply.

Sesamoid bones are often present in tendons that wrap around bony pulleys or cross synovial joints (Williams et al., 1995). Well-known sesamoids that are constantly present include the patella in the quadriceps tendon, the pisiform in the tendon of flexor carpi ulnaris, and the sesamoids within the tendons of flexor hallucis brevis, adductor pollicis and flexor pollicis brevis. In addition, occasional sesamoids are found in a large number of tendons e.g. the lateral head of gastrocnemius and peroneus longus.

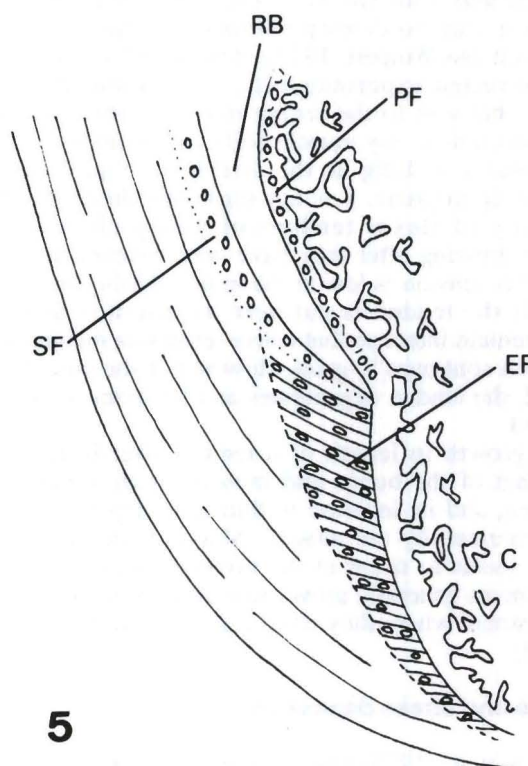
### Entheses

The junction between a tendon/ligament and bone is called an 'enthesis' - a term widely used in rheumatology texts. There are 2 forms of entheses - fibrous and fibrocartilaginous and they have been recently reviewed by Benjamin and Ralphs (1995). Briefly, fibrous attachments are found on the metaphyses and diaphyses of long bones and correspond to the 'indirect insertions' of Woo et al. (1988). Fibrocartilaginous entheses are typical of epiphyses and apophyses and correspond to the 'direct insertions' of Woo et al. (1988). In fibrous entheses, the collagen fibres of the ligament/tendon attach to the periosteum during the growing period or directly into the bone in adults. In fibrocartilaginous entheses, there is a transitional zone of fibrocartilage at the bone junction (Fig. 4) so that there are characteristically 4 zones of tissue at the enthesis - fibrous connective tissue, uncalcified fibrocartilage, calcified fibrocartilage and bone (Benjamin and Ralphs, 1995).

Enthesis fibrocartilage is just one of a series of protective devices to reduce wear and tear. At many tendon attachment sites e.g. the Achilles (Rufai et al. 1995), it is accompanied by (1) a small synovial bursa that allows the tendon to move freely relative to the bone, (2) a sesamoid fibrocartilage on the deep surface of the tendon and a periosteal fibrocartilage on the bone that protects the tendon/ligament where they rub against each other (Fig. 5). All 3 of these fibrocartilages can be the site of degenerative changes ('enthesopathies'). There is frequently fissuring, fragmentation and degeneration of the sesamoid and periosteal fibrocartilages either side of the retrocalcaneal bursa. Where the superior tuberosity of the calcaneus is prominent, the sesamoid and periosteal fibrocartilages are well developed and signs of pathology are more frequent (Rufai et al. 1995). Thus it seems likely that in patients with Haglund's deformity (where there is an exostosis on the superior tuberosity- Haglund, 1928) there is tendon and periosteal fibrocartilage degeneration.

Bony spurs develop at many tendon/ligament entheses and such heterotopic ossification is a basic feature of ankylosing spondylitis. In the Achilles tendon, Rufai et al. (1995) have shown that the spurs develop by endochondral ossification within enthesis fibrocartilage. Other pathologies characterise this tissue as well. One of

the most striking is the presence of longitudinal fissures that resemble those seen in articular cartilage in the early stages of osteoarthritis (Rothwell and Bentley, 1973). In both the tendon and articular cartilage, there are clusters of large, rounded cells at the edges of fissures. It is particularly noteworthy that in the tendon, the clusters were restricted to the fibrocartilage region (Rufai et al., 1995). Where the fissure extends into the tendon proper, there is no cartilage cell response. An obvious difference between the fissures in the Achilles tendon and those in articular cartilage is that the former are filled with amorphous metachromatic material or a poorly organised fibrous ECM and that radiographs showed that these regions were often calcified. It seems likely that the contents of the fissures represent an attempted repair response. It could be that similar material is absent from cartilage fissures because these open onto the joint cavity and are thus washed out. Transverse tears at the enthesis of the Achilles tendon are very different (Rufai et al., 1995). They are small, occur at the junction of calcified and uncalcified regions of fibrocartilage and are filled with loose vascular connective tissue. There is no obvious cell response.



**Fig. 5.** Diagrammatic representation of the 3 protective devices at the attachment of the human Achilles tendon to the calcaneus (C). Enthesis fibrocartilage (EF) dissipates stress at the insertion site and ensures that collagen fibres in the tendon bend gradually with ankle movements; the retrocalcaneal bursa (RB) facilitates free play between tendon and bone during dorsiflexion, and the sesamoid (SF) and periosteal (PF) fibrocartilages protect both the tendon and the bone where they rub against each other.



### Growth and development

Some of the most significant work on growth and development relates to tendons of the digits (Greenlee and Ross, 1967). These start to form at approximately the same time as the cartilaginous phalanges and their future position is marked by tenascin-rich sheets of ECM beneath the ectodermal basal lamina (Hurlé et al., 1989; Ros et al., 1991). The early tendon is highly cellular and the longitudinal rows of cells become separated by ECM. Collagen synthesis begins intracellularly, but is continued in the ECM under cellular control. Birk and colleagues (see Birk and Zycband, 1994 for review) have described 3 levels of matrix organisation in the ECM - (a) small channels in the tendon cell surface containing 1-3 collagen fibres (b) larger bundles of fibres enclosed in cell surface folds and (c) the rest of the ECM where fibre bundles have become grouped together away from the vicinity of the folds. The confocal microscopy studies of McNeilly et al. (1996) suggest that there is also a fourth compartment that is formed by cells in the same longitudinal row that have sheet-like processes enclosing the same fibre bundle.

The initial development of a tendon is independent of its muscle and if the two are prevented from interacting, the tendon starts to develop normally but later regresses (Shellswell and Wolpert, 1977). If the tip of a chick limb bud is inverted experimentally, the tendons develop normally but join to the wrong muscles. This suggests that connection to any muscle belly can promote tendon development so long as the direction of pull of the muscle is appropriate. It is not surprising therefore, that the ability of flexor tendons of young chickens to continue growing after they have been severed depends on whether tension is lost in the injury (Nishijima et al., 1995). If the tendon is cut near its insertion and the vinculi remain intact so that active tension is maintained, the tendon continues to grow. However, if the vinculi are ruptured, the tendon degenerates and becomes markedly shortened.

The growth in length of a tendon after birth must match that of the bones and muscles with which it is associated, and its increase in thickness depends on the force generated by the muscle. Much of the growth of tendons seems to occur at the myotendinous junctions, but ligaments generally grow more uniformly along their length, except where they cross a growth plate (Frank et al., 1988).

### Exercise and stress deprivation

Tipton et al. (1975) have shown that 10 week periods of exercise training significantly increases the weight and size of ligaments and prolonged immobilisation of limbs is known to reduce ligament strength (Akeson et al., 1987; Woo et al., 1990). Some ligaments are more susceptible to immobilisation than others. The ACL is more vulnerable than the medial collateral ligament (MCL). During periods of immobilisation, the normally

fibrocartilaginous cells of the ACL become fibroblastic and there are significant reductions in the mechanical strength of the femur-ACL-tibia complex (Woo et al., 1990). Similar findings have also been documented for tendons. According to Murrell et al. (1994), immobilisation of severed rat Achilles tendons had a pronounced and detrimental effect on the mechanical properties of the tendon-calcaneal complex.

AbiEzzi et al. (1995) have shown that stress deprivation is associated with increased expression of  $\beta 1$ ,  $\alpha 5$  and  $\alpha v$  integrins in both the ACL and MCL of rabbits. The time course of the changes suggest that these integrins play an important role in the remodelling of the ECM that occurs in stress-deprived ligaments. Growth factors are known to promote the formation of ECM and thus encourage wound healing. The *in vitro* studies of Lee et al. (1995) on explants of the MCL and ACL suggests that the application of combinations of growth factors (bFGF, TGF- $\beta 1$ , PDGF-B and bovine insulin) enhances the healing of both ligaments to a greater extent than does the application of a single growth factor alone.

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