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## Review

# Fibrocartilage in tendons and ligaments—an adaptation to compressive load

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ABSTRACT

Where tendons and ligaments are subject to compression, they are frequently fibrocartilaginous. This occurs at 2 principal sites: where tendons (and sometimes ligaments) wrap around bony or fibrous pulleys, and in the region where they attach to bone, i.e. at their entheses. Wrap-around tendons are most characteristic of the limbs and are commonly wider at their point of bony contact so that the pressure is reduced. The most fibrocartilaginous tendons are heavily loaded and permanently bent around their pulleys. There is often pronounced interweaving of collagen fibres that prevents the tendons from splaying apart under compression. The fibrocartilage can be located within fascicles, or in endo- or epitenon (where it may protect blood vessels from compression or allow fascicles to slide). Fibrocartilage cells are commonly packed with intermediate filaments which could be involved in transducing mechanical load. The ECM often contains aggrecan which allows the tendon to imbibe water and withstand compression. Type II collagen may also be present, particularly in tendons that are heavily loaded. Fibrocartilage is a dynamic tissue that disappears when the tendons are rerouted surgically and can be maintained in vitro when discs of tendon are compressed. Finite element analyses provide a good correlation between its distribution and levels of compressive stress, but at some locations fibrocartilage is a sign of pathology. Enthesis fibrocartilage is most typical of tendons or ligaments that attach to the epiphyses of long bones where it may also be accompanied by sesamoid and periosteal fibrocartilages. It is characteristic of sites where the angle of attachment changes throughout the range of joint movement and it reduces wear and tear by dissipating stress concentration at the bony interface. There is a good correlation between the distribution of fibrocartilage within an enthesis and the levels of compressive stress. The complex interlocking between calcified fibrocartilage and bone contributes to the mechanical strength of the enthesis and cartilage-like molecules (e.g. aggrecan and type II collagen) in the ECM contribute to its ability to withstand compression. Pathological changes are common and are known as enthesopathies.

*Key words*: Enthesis; extracellular matrix; aggrecan; type II collagen.

## INTRODUCTION

Tendons serve primarily to transfer the pull of muscles to bone while ligaments connect one bone to another. Both are characterised by their great tensile strength and are dominated by collagen fibres. However, tendons and ligaments have dynamic characteristics that belie their appearance—they are capable of repair after injury and respond to exercise or immobilisation by altering their tensile strength (Frank et al. 1988; Woo et al. 1988). This dynamic behaviour suggests that the cells in tendons and ligaments are capable of detecting changes in mechanical load and co-ordinating their response to alter the composition of the extracellular matrix (ECM). One of the most obvious ways in which the ECM of tendons and

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ligaments is modified in response to load is by the formation of a fibrocartilaginous matrix at sites where the tendons or ligaments are under compression. This occurs where they change direction by wrapping around bony pulleys or threading through fibrous retinacula, and where they attach to bone.

## BASIC PRINCIPLES OF TENDON/LIGAMENT STRUCTURE

At the microscopic level, tendons and ligaments consist of cells that are generally arranged in longitudinal rows separated by collagen fibres and proteoglycan threads and granules. Even in the tensional regions of tendons and ligaments, their cells have an elaborate shape. In the digital flexor tendons of rat hind limbs, broad, flat processes enclosing bundles of collagen fibres extend laterally from the cell bodies to contact the processes of adjacent cells via gap junctions (McNeilly et al. 1996). The cell bodies of neighbouring cells in a longitudinal row also communicate with each other by gap junctions, and thus there is a continuous 3D cellular network that pervades throughout the tendon. This could provide the basis by which tendons or ligaments detect mechanical load and coordinate their cellular response to it.

Unfortunately, the terminology used to describe the arrangement of collagen fibres is often confused. Thus it is frequently unclear what an author means by a 'fibril', 'fibril bundle', 'fibre' or 'fascicle' or whether, for example, the 'epitenon' of one author is equivalent to the 'peritendineum' of another. The terminology we adopt here is essentially similar to that used by Viidik (1966). Thus we regard collagen *fibrils* as being those clearly visible in low power electron micrographs and *fibres* as bundles of fibrils seen in light micrographs. In developing tendons, both fibrils and fibres form in intimate association with the tendon cells themselves (Birk & Zycband, 1994). Fibrils initially lie singly or in small groups in shallow recesses on the surfaces of tendon cells and become aggregated into fibres as they move away from the cell surface into larger compartments created by the laterally-directed processes of tendon cells. *Fibre bundles* are collections of fibres separated from other bundles by tendon/ligament cells alone, while *fascicles* are larger collections of fibres or fibre bundles that are surrounded by loose connective tissue septa called *endotenon*. Hence the presence of septa within a tendon or ligament can be taken as an indication of the existence of fascicles. This is in agreement with the descriptions by Clark & Sidles (1990) of fasciculation in the anterior cruciate ligament. Not all tendons are multifascicled—many of those in rats are just a single fascicle (Benjamin & Ralphs, unpublished observations). The distinction made by some authors between *primary*, *secondary* and *tertiary* fascicles is based on variations in the prominence of the septa (Kastelic et al. 1978). The septa are most conspicuous around the tertiary fascicles and least obvious around the primary ones, although the distinction is often difficult to apply (Clark & Sidles, 1990). The essential point is that the fibres in a fascicle are associated with more than one tendon/ligament cell and are wrapped together in endotenon/endoligament. The latter probably develops in conjunction with the vascularisation of the tendon/ligament primordium and this seems to happen around E13–14 in chick embryos (McBride et al. 1985). In the larger, multifascicled tendons/ligaments, there is a surrounding sheath of connective tissue that encloses the whole structure, the *epitenon* or *epiligament*. This is directly continuous with the endotenon/endoligament and the points of continuity help to bind it firmly to the surface of the tendon or ligament itself. Finally, the *paratenon* is a false tendon sheath, quite separate from the tendon itself and consisting of a condensation of the surrounding loose connective tissue through which the tendon moves. No equivalent structure has been documented for ligaments. Presumably fascicles can move over each other when a tendon/ligament is loaded (Clark & Sidles, 1990) and their presence reduces the risk of catastrophic failure and allows a tendon/ligament to adapt its form and shape in response to the tensile, compressive or shearing forces that deform it. Fibrocartilaginous specialisations of tendons/ligaments can be manifest at all levels of their hierarchical organisation, fibril diameter, fascicle organisation and the prominence and character of the endotenon, epitenon and paratenon.

## FIBROCARTILAGE IN WRAP-AROUND TENDONS AND LIGAMENTS

The term 'wrap-around tendon' was introduced by Alexander & Dimery (1985) to describe 1 of 3 different mechanisms for extensor tendon insertion, via a retroarticular process, by attaching to a sesamoid bone, or by wrapping around the joint just proximal to the attachment site (Benjamin et al. 1995). The term is now applied more generally to any tendon that bends around a bony pulley or threads through a fibrous one en route to its insertion. Tendons that run

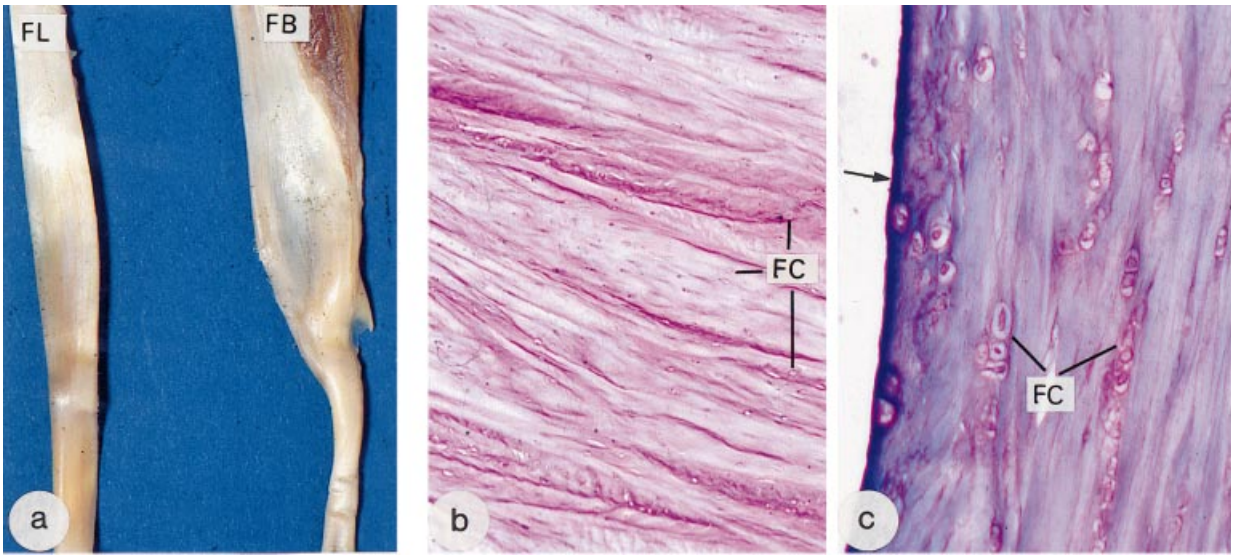


Fig. 1. Fibrocartilage in wrap-around tendons and their pulleys. (*a*) Flattening of the tendons of fibularis (peroneus) longus (FL) and fibularis (peroneus) brevis (FB) in the region where they wrap around the lateral malleolus. The flattened region is more obvious in fibularis brevis as this lies between the malleolus and fibularis longus and is thus compressed from both sides. Neither tendon shows evidence of fissuring. (*b*) The highly fibrocartilaginous region of the tendon of fibularis longus where it grooves the cuboid. Note the strong metachromasia and the basketweave arrangement of collagen fibres in this low power view. The fibrocartilage cells (FC) are just visible. Toluidine blue $\times 40$. (*c*) High power view of fibrocartilage in the inferior peroneal retinaculum against which the fibularis longus tendon presses as it wraps around the peroneal trochlea of the calcaneus. The surface of the retinaculum in contact with the tendon is indicated by an arrow. Note the prominent fibrocartilage cells (FC) and their surrounding metachromatic, pericellular ECM. Toluidine blue, $\times 320$.

a straight course from muscle to bone are referred to as 'direct tendons' in the current review. Some ligaments (e.g. the annular ligament of the radius and the transverse ligament of the atlas) also 'wrap around' or are compressed against bone. Wrap-around tendons/ligaments and their pulleys are frequently fibrocartilaginous, and a basic premise of the current review is that this is an adaptation to compression (Vogel & Koob, 1989; Vogel, 1995).

Giori et al. (1993) have made a useful comparison between a tendon that changes direction around a bone and a strap that wraps around a pulley. When a tensile force ($T$) is applied to a strap of width $w$, the contact pressure $P$ applied to the strap is given by the equation $P = T/rw$—where r is the radius of the pulley. Thus in the context of a musculotendinous unit, the reactive pressure is highest when the muscle exerts great tension, the pulley is small and the tendon is narrow. This explains why tendons often become flattened at the point where they press against bone (Fig. 1*a*; Meyer et al. 1964). Many tendons are also known to slide longitudinally over the bone as they press against it and thus might be expected to contain an extended length of fibrocartilage. On the other hand, as Giori et al. (1993) have argued, the strongest muscle contraction may occur when approximately the same region of tendon contacts the bone. This may remove the requirement for an extended length of fibrocartilage.

Where the longitudinal excursion of a tendon is significant, for example in the flexor tendons of the fingers (Chao et al. 1989), there is also considerable friction between the tendon and its pulley. The frictional forces are directly related to the tension in the tendon and the angle of the arc of contact between tendon and pulley (An et al. 1995).

### *Location of wrap-around tendons/ligaments*

A comprehensive list of wrap-around tendons is given by Benjamin et al. (1995). Most are found in the limbs and are especially common in the foot. They are generally long and cord-like and inevitably their muscle bellies are situated some distance from the bone to which the tendons attach. Occasional wrap-around tendons link 2 muscle bellies together (e.g. digastric or omohyoid) rather than linking muscle to bone. One can distinguish between those that always change direction whatever the position of the limb (e.g. any tendon wrapping around the malleoli of the ankle) and those that only change direction when the limb is in certain positions (e.g. many tendons at the wrist). Fibrocartilage is more characteristic of the former (Benjamin et al. 1995). The ankle tendons are more markedly bent around their pulleys and are associated with more powerful muscles that compress the tendons against the bone with greater force. A distinction can also be made between tendons that

wrap around bony pulleys some considerable distance from their insertion (e.g. fibularis [peroneus] longus) and those where the pulley is very close to the enthesis, e.g. the Achilles tendon, where the superior tuberosity of the calcaneus acts as a pulley for the tendon when the foot is dorsiflexed (Benjamin et al. 1995).

Not all wrap-around tendons are fibrocartilaginous, and a notable exception is that of the superior oblique muscle of the eye. Although this tendon changes direction abruptly as it threads through the trochlea (a small pulley near the superomedial part of the orbit), it retains the characteristics of a direct tendon (Benjamin et al. 1995). However, the pulley itself is strikingly cartilaginous and the excursion of the tendon is aided by a synovial sheath. Nonfibrocartilaginous, wrap-around tendons in the limbs are those that only change direction when the limb is in certain positions (Benjamin et al. 1995). They include the flexor and extensor tendons at the wrist that act largely as direct tendons when the hand is in the neutral position of rest. In contrast, tendons at the ankle that wrap around the malleoli are distinctly fibrocartilaginous, as they are constantly bent around bony pulleys and are under heavier load.

### *Macroscopic structure*

Meyer et al. (1964), Sick (1964) and Ribot (1967) have listed a number of macroscopic structural adaptations of wrap-around tendons and ligaments that are in broad agreement with the earlier work of Ploetz (1938). There may be parallel fissures that subdivide the tendons thus allowing them to mould their form and shape to the pulley surface as they become loaded by muscle contraction. However, this is not obvious in the peroneal tendons that wrap around the malleoli (Fig. 1*a*). The epitenon is frequently thickened and there are also characteristic patterns of fasciculation (Meyer et al. 1964). Nearer to the surface subject to compression, the fascicles are small, flat and separated by very little endotenon. Beneath them is a collection of much larger and more rounded fascicles that are surrounded by thicker connective tissue partitions and which are the only type of fascicle found in direct tendons. Several authors have commented that fascicles in fibrocartilaginous regions of tendons are arranged spirally and bound to each other by cross connections (Achilles tendon, Cummings et al. 1946; the tendons of flexor digitorum superficialis and profundus, Martin, 1958; and flexor pollucis longus, Hueston & Wilson, 1972). The interweaving of collagen fibres in wrap-around tendons (Fig. 1*b*) must mean that tensile forces are spread throughout the width of the tendon at all points distal to the bony contact site, even when the muscles operate at low tension levels.

### *Fibrocartilage structure and composition*

Fibrocartilage in wrap-around tendons can be located either within the fascicles themselves (Fig. 1*b*), or within the epitenon or endotenon (Benjamin et al. 1995). Proteoglycans may even accumulate in the endotenon in the absence of fibrocartilage cell differentiation (Berenson et al. 1996). The variety of forms of fibrocartilage suggest that there is a continuous spectrum of tissues between dense fibrous connective tissue and hyaline cartilage. Perhaps fibrocartilage in the epitenon or endotenon may represent a moderate form of differentiation that protects tendon vasculature or allows fascicles to slide over one another in particularly malleable parts of the tendon. Where fibrocartilage is present within fascicles, the large fibrocartilage cells can be surrounded by an interwoven network of collagen fibres or lie in rows between parallel fibres (Benjamin et al. 1995). The differences probably relate to how the fibrocartilage develops in the first place (Benjamin & Ralphs, 1995). It seems likely that any interwoven basketweave arrangement of collagen fibres is established early in development when the tendon is highly cellular. It is difficult otherwise to imagine how a relatively small number of mature tendon cells could orchestrate the necessary matrix turnover.

Fibrocartilage cells are large and oval and often packed with intermediate filaments (IFs; Merrilees & Flint, 1980; Ralphs et al. 1991). There is some evidence to suggest that IFs could be involved in the transduction of mechanical load via interactions between the cytoskeleton, integrins in the cell membrane and the ECM (Benjamin et al. 1994). IFs are particularly characteristic of the midzone of articular cartilage, especially in weight-bearing regions (Eggli et al. 1988) and are also known to accumulate in endothelial cells that are subjected in culture to intermittent hydrostatic pressure (Schnittler et al. 1993). Durrant (1997) has recently shown that IFs disappear from full thickness shavings of articular cartilage during the first hour of culture, but that this can be prevented by keeping the shavings under a static load of 1 MPa or more. During the differentiation of tendon fibrocartilage cells, they accumulate at a time that corresponds to increasing mechanical loads (Ralphs et al. 1992).

The GAG content of wrap-around tendons is much higher than that of direct tendons that are subject only to tension (Vogel et al. 1993; Koob & Vogel, 1987). Much of the GAG is probably associated with the large, aggregating proteoglycan aggrecan that is characteristic of articular cartilage (Vogel et al. 1994; Vogel, 1995; Perez-Castro & Vogel, 1998). The many glycosaminoglycan (GAG) side chains attached to the core proteins of aggrecan that are in turn linked to a central hyaluronan molecule, create a high negative charge density so that domains are formed with a high osmotic pressure (Heinegård & Oldberg, 1993). Consequently, the presence of aggrecan in a tendon greatly increases its capacity to imbibe water and thus to withstand compression.

The ECM of tendon fibrocartilage is rich in small-diameter collagen fibres (Merrilees & Flint, 1980). Type II collagen is frequently present, although there are often variations in man, both between different wrap-around tendons and between the same tendon in different individuals. Thus type II collagen is only expressed in the extensor tendons of some fingers (Benjamin et al. 1993), but is more commonly seen in the toes, perhaps because the extensor tendons here are more heavily loaded and more constantly compressed against the heads of the proximal phalanges (Milz et al. 1998). Furthermore, type II collagen is less characteristic of extensor hallucis, perhaps because the interphalangeal joint of the 1st toe is commonly extended in the standing position (Milz et al. 1998). There are also marked species differences in tendon fibrocartilages. The sesamoid fibrocartilage in the quadriceps tendon of the rat (the suprapatella) only accumulates type II collagen in old animals, but in the mouse, the same fibrocartilage shows strong immunolabelling soon after birth (Ralphs et al. 1994).

### *Significance of fibrocartilage*

There is abundant evidence to support the contention that fibrocartilage in wrap-around tendons is an adaptation to compression. It is a prediction that arises directly from Pauwels's (1960) causal theory of histogenesis and perhaps the most compelling support comes from the experimental studies of Ploetz (1938) and Gillard et al. (1979), reconfirmed recently by Malaviya et al. (1996). Ploetz (1938) surgically translocated a 'direct' tendon so that it was made to wrap around a bony pulley in a rabbit's foot and also did the converse procedure of converting a wrap-around tendon into a direct one. In the first experiment, cartilage cells appeared in the tendon and in the second, they disappeared. As Pauwels (1960) has pointed out, it is significant that the cartilage cells in Ploetz's (1938) first experiment only appeared on the side of compression. They did not develop on the outer aspect of the tendon, where there is shear but no compression. In a related series of experiments, Gillard et al. (1979) showed that the total GAG content of a wrap-around tendon that had been surgically converted into a direct one, was rapidly reduced to the low levels typical of direct tendons. Although the GAGs were slowly replenished when the tendon was restored to its original position, the recovery diminished the longer the tendon was left at its translocated site. Direct evidence linking fibrocartilage development to compressive forces has also come from in vitro studies on discs of adult bovine tendon fibrocartilage (Koob et al. 1992). Aggrecan synthesis was rapidly lost from unloaded control discs but maintained when cyclic uniaxial compression was applied. Furthermore, when fetal tendons were loaded in vitro, the synthesis of aggrecan and biglycan was actually increased, as were their levels of mRNA expression (Evanko & Vogel, 1993). The presence of fibrocartilage in a wrap-around tendon leads to the development of a region of low permeability where the tendon contacts the bone (Wren et al. 1998). This reduces the stresses imposed on the collagen fibres by slowing the rate of stress transfer from the fluid to the solid components of the ECM.

The degree of fibrocartilage differentiation in a tendon varies according to the distance from the bony surface against which the tendon is compressed (Ploetz, 1938; Meyer et al. 1964; Merrilees & Flint, 1980). The finite element analyses of Giori et al. (1993) and Haridas et al. (1998) show that regions where fibrocartilage is present in the rabbit flexor digitorum profundus tendon, correlate well with areas of high compressive stress. It seems that the peak hydrostatic stress in wrap-around tendons is similar to the contact pressure articular cartilage experiences in vivo.

The presence of fibrocartilage within tendons is viewed by some pathologists as synonymous with mucoid degeneration and considered a prelude to tendon rupture or calcifying tendinitis (Uhthoff & Sarkar, 1991). It seems that degeneration and tearing of several tendons is associated with pronounced fibrocartilaginous metaplasia, perhaps in response to enhanced activity of matrix metalloproteinases (Chard et al. 1993; Riley et al. 1996). As the fibrocartilage develops, high levels of aggrecan and biglycan accumulate locally and this may lower the ultimate tensile strength of the tendon (Berenson et al. 1996; Flatow et al. 1998). According to some authors the fibrocartilaginous metaplasia is triggered by poor

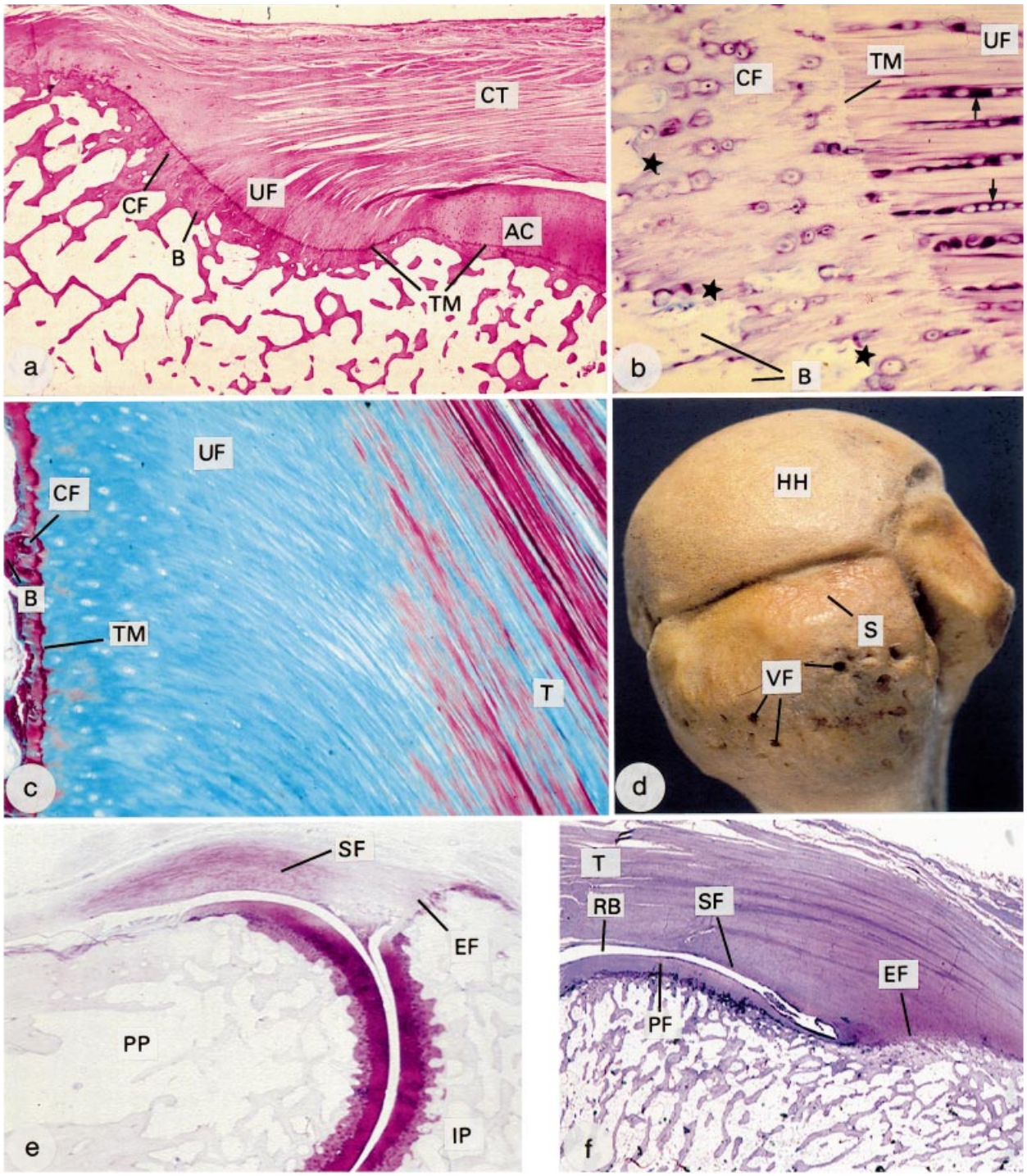


Fig. 2. The normal structure of fibrocartilaginous entheses. (*a*) The 4 zones of tissue at the insertion of the human supraspinatus tendon: dense fibrous connective tissue (CT), uncalcified fibrocartilage (UF), calcified fibrocartilage (CF) and bone (B). The calcified and uncalcified fibrocartilage are separated by a tidemark (TM) that is straight and continuous with a similar tidemark in the adjacent articular cartilage (AC) on the humeral head. H & E, ×8. (*b*) Enthesis fibrocartilage at high power showing the longitudinal rows of cells (arrows) in the uncalcified fibrocartilage (UF) that are surrounded by pericellular metachromatic matrix. Note also that the junction between the calcified fibrocartilage (CF) and the bone (B) is highly irregular (asterisks), but that the tidemark (TM) is straight. Insertion of the rat quadriceps tendon into the patella. Toluidine blue, ×180. (*c*) The collagen fibres in the tendon (T) gradually change in direction as they sweep through the zone of uncalcified fibrocartilage (UF) towards the bone (B). Note also that their staining properties change—from red in the tension-bearing dense fibrous connective tissue to green in the zone of uncalcified fibrocartilage. CF, calcified fibrocartilage; TM, tidemark (TM). Insertion of the human Achilles tendon onto the calcaneus. Masson's trichrome, ×60. (*d*). The marking left on the greater tuberosity of the humerus by the tendon of supraspinatus (S) is similar to that left by articular cartilage on the adjacent humeral head (HH). Both are smooth, circumscribed and devoid of vascular foramina (VF). A comparison with *a* helps in understanding why the markings are similar. The soft tissues fall away during maceration at the level of the tidemark (TM in *a*), which is straight and continuous from enthesis to articular cartilage. Hence the markings in *d* are smooth. The markings lack vascular foramina because both the enthesis fibrocartilage and the articular

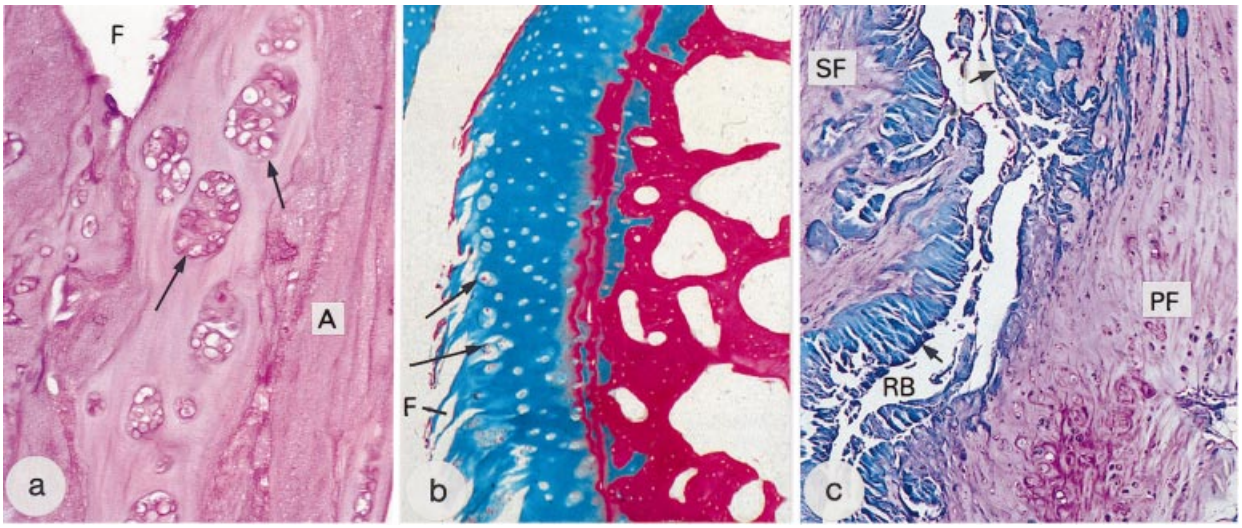


Fig. 3. Pathology at tendon attachment zones. (*a*) Clusters of cartilage cells (arrows) at the edge of a longitudinal fissure in the enthesis fibrocartilage of a human Achilles tendon. Parts of the fissure are filled with amorphous, metachromatic repair material (A). ×120. (*b*) Fissures (F) and clustering of cartilage cells (arrows) in the early stages of osteoarthritis in a human metatarsophalangeal joint to show the similarities with fissure formation in tendons (compare with *a*). Masson's trichrome, ×30. (*c*) Degeneration of the sesamoid (SF) and periosteal (PF) fibrocartilages of the human Achilles tendon and the detachment of the tissue fragments into the retrocalcaneal bursa (RB). Note the change in the staining properties of both fibrocartilages (arrows) adjacent to the bursa. Toluidine blue, ×50.

blood supply of the tendon (see Józsa & Kannus, 1997 for a review). However, other authors consider avascularity to be a normal consequence of fibrocartilage development (e.g. Koch & Tillmann, 1995). Although it does seems likely that fibrocartilage can develop pathologically within tendons, we consider that tendon fibrocartilage should primarily be viewed as a tissue that develops normally in response to compression. Blevins (1996) too has cautioned against the view that fibrocartilage in a tendon must always be a sign of degeneration. Nevertheless, the presence along the length of a healthy tendon of local regions of fibrocartilage is likely to affect the repair process if the tendon is damaged. Fibrous and fibrocartilaginous regions of a tendon respond differently in the extent of their cell division and matrix synthesis to the addition of growth factors that are aimed to encourage repair (Abrahamsson & Lohmander, 1996).

### *Pulley fibrocartilage*

Where a tendon is compressed against a pulley, there is an equal and opposite force acting on the bone or fibrous retinaculum. Any tendon with a marked longitudinal excursion also has a significant 'sawing' action by virtue of the shearing forces it applies. Although the presence of lubricating synovial sheaths reduces friction, the bony or fibrous pulleys are also frequently fibrocartilaginous (Stilwell & Gray, 1954; Benjamin et al. 1995). For bony pulleys, the fibrocartilage is a modified periosteum and there is often a close correlation between the extent of fibrocartilage differentiation here and that in the tendon (Benjamin et al. 1995). Thus the most fibrocartilaginous tendon in man (fibularis longus) wraps around the most fibrocartilaginous pulley (the groove on the cuboid). It seems that the presence of a tendon in contact with a bone is necessary to maintain a periosteal fibrocartilage. Where the tendon of the long head of biceps brachii is ruptured in the intertubercular sulcus, the periosteal fibrocartilage disappears (Benjamin et al. 1992*a*). This suggests that mechanical factors are necessary for maintaining a fibrocartilaginous phenotype.

Occasionally, fibrocartilage is more conspicuous in a fibrous pulley than in the corresponding region of

cartilage are avascular. (*e*) A metachromatic sesamoid fibrocartilage (SF) on the deep surface of the central slip of the extensor tendon of a human finger. It articulates with the proximal phalanx (PP) when the finger is flexed and lies adjacent to the enthesis fibrocartilage (EF). A sagittal section through the proximal interphalangeal joint of a human finger stained with toluidine blue. IP, intermediate phalanx. ×7. (*f*) The 3 fibrocartilages that reduce wear and tear at the attachment of the human Achilles tendon (T). In addition to enthesis fibrocartilage (EF), there is a sesamoid fibrocartilage (SF) on the deep surface of the Achilles tendon and a periosteal fibrocartilage (PF) on the calcaneus. These protect the bone and tendon, where they press against each other during dorsiflexion of the foot. The free movement of the tendon is promoted by the retrocalcaneal bursa (RB). Sagittal section, toluidine blue, ×4.

the associated tendon, e.g. the inferior peroneal retinaculum (Fig. 1*c*) or the pulley for the superior oblique muscle of the eye (Benjamin et al. 1995). It is intriguing to note that during the surgical reconstruction of fibrous pulleys using expanded polytetrafluorethylene (e-PTFE), Hanff & Abrahamsson (1996) found that the xenograft became infiltrated with cells that show high rates of proteoglycan synthesis, suggesting the formation of a fibrocartilaginous matrix.

## FIBROCARTILAGE AT ENTHESES

The term 'enthesis' is commonly used in rheumatology to denote the junction between a tendon or ligament and a bone. It has long been known that there are 2 fundamentally different types of entheses according to the presence or absence of fibrocartilage at the attachment sites. We have called the 2 types of entheses *fibrocartilaginous* and *fibrous* (Benjamin & Ralphs, 1995), but others have called them chondral and periosteal (Knese, 1979) or direct and indirect (Woo et al. 1988). Typically tendons/ligaments that attach to the epiphyses of long bones or to the short bones of the tarsus or carpus have fibrocartilaginous entheses (Fig. 2), whereas those that attach to metaphyses or diaphyses have purely fibrous insertions (Schneider, 1956; Benjamin & Ralphs, 1995). Where enthesis fibrocartilage is found at a tendon insertion, other fibrocartilages may accompany it because of the close proximity of such entheses to highly mobile synovial joints. Thus in the proximal interphalangeal joints of the fingers and toes, there is a sesamoid fibrocartilage on the deep surface of the extensor tendon that is adjacent to the enthesis fibrocartilage and which 'articulates' with the proximal phalanx when the joint is flexed (Fig. 2*e*; Benjamin et al. 1993; Lewis et al. 1998; Milz et al. 1998). The extent of cartilage differentiation is greater in the toes than the fingers, perhaps because the toes are more constantly flexed as they grip the ground during gait and because their extensor tendons have larger muscles that are more heavily loaded. There is also a sesamoid fibrocartilage on the deep surface of the Achilles tendon where the tendon presses against the superior tuberosity of the calcaneus in a dorsiflexed foot (Fig. 2*f*; Rufai et al. 1992, 1995). The bone itself is protected from compression by a periosteal fibrocartilage on the tuberosity and is separated from the tendon by the retrocalcaneal bursa (Fig. 2*f*; Rufai et al. 1992, 1995). Thus there may be a whole series of protective devices at fibrocartilaginous entheses that reduce the risk of wear and tear. Nevertheless, degenerative changes are still common and are known as enthesopathies, e.g. tennis elbow, golfer's elbow and jumper's knee. A histological survey of enthesopathies in the Achilles tendon of elderly human cadavers showed that degenerative changes were very common and affected all 3 fibrocartilages (Rufai et al. 1995). The changes included bony spurs and calcified fissures in the enthesis fibrocartilage, and partial delamination and fragmentation of the sesamoid and periosteal fibrocartilages into the retrocalcaneal bursa (Fig. 3).

### *Structure*

The basic structure of fibrocartilaginous entheses was established by Dolgo-Saburoff (1929) and by Cooper & Misol (1970). They both described a sequence of 4 zones of tissue at the attachment of the quadriceps tendon/patellar ligament: dense fibrous connective tissue, uncalcified fibrocartilage, calcified fibrocartilage and bone (Fig. 2*a–c*). The zones of calcified and uncalcified fibrocartilage are separated from each other by a line called the tidemark which lies at the outer limit of calcification (Fig. 2*a–c*). It is often intensely basophilic and is where the soft tissues fall away from the bone after maceration (Benjamin et al. 1986). At the EM level, the tidemark appears as an electron dense layer of granular material (Rufai et al. 1996). As it is straight, not crossed by blood vessels and continuous with a similar tidemark beneath adjacent articular cartilage, the markings left on a dried bone by fibrocartilaginous entheses resemble those left by articular cartilage (Benjamin et al. 1986). Both are smooth, circumscribed and devoid of vascular foramina (Fig. 2*d*). Tendon/ligament failure at fibrocartilaginous entheses most often occurs both clinically and experimentally in the subchondral bone, suggesting that the bone itself is weaker than the transitional region between hard and soft tissues (Woo et al. 1988; Gao et al. 1996*a*).

Fibrocartilage is not equally conspicuous over the entire enthesis but is thickest in its deep part and absent superficially (Benjamin et al. 1986; Woo et al. 1988; Frowen & Benjamin, 1995). This is in line with the finite element model of Matyas et al. (1995) that correlates the greater development of fibrocartilage in the deep part of an enthesis with where the highest levels of compressive stress are predicted. The cells in the zone of uncalcified fibrocartilage are rounded or oval, and typically arranged in longitudinal rows separated by parallel collagen fibres (Fig. 2*b*). The

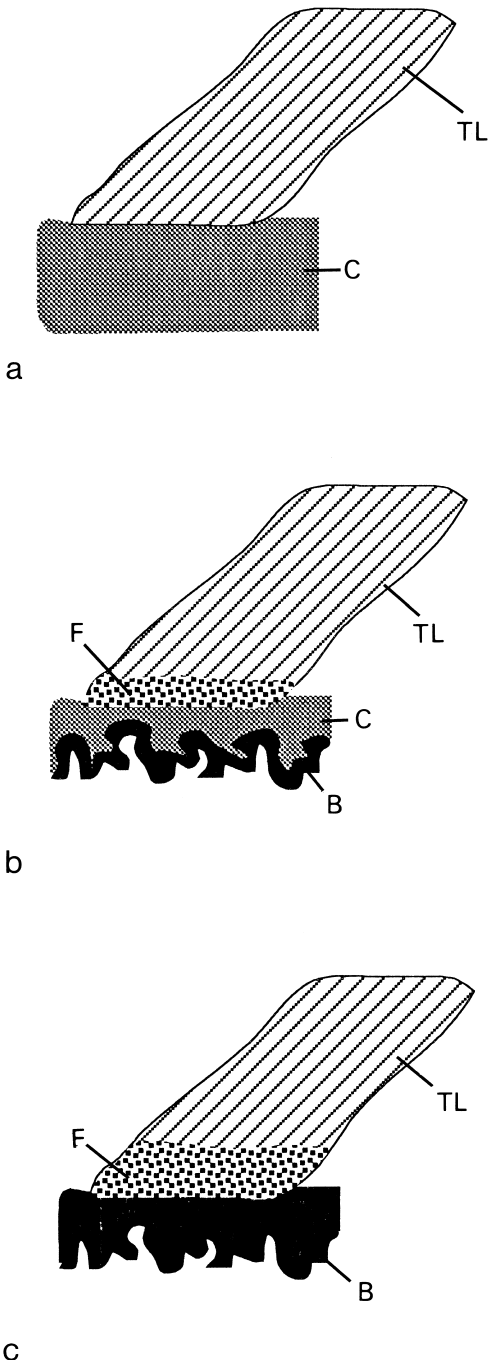


Fig. 4. Diagrammatic representation of 3 stages in the development of enthesis fibrocartilage (based on Gao et al. 1996*b*). (*a*) The tendon or ligament (TL) initially attaches to an entirely cartilaginous (C) bone anlage. (*b*) Later, as the cartilage is eroded during endochondral ossification and is partly replaced by bone (B), enthesis fibrocartilage (F) develops by metaplasia of tendon or ligament cells. (*c*) Finally, as all the original cartilage is replaced by bone, the metaplastic enthesis fibrocartilage extends further into the tendon or ligament.

fibrocartilage cells are isolated within the ECM, for in contrast to the midsubstance of a tendon/ligament, they do not communicate with each other via gap junctions (Ralphs et al. 1998). Thus enthesis fibrocartilage acts as a barrier to communication between the network of communicating osteocytes in the bone and the fibroblasts that communicate with each other in the tendon. The significance of this barrier and of the lack of vascular communication between tendon/ligament and bone is unclear.

Enthesis fibrocartilage cells are surrounded by a metachromatic pericellular matrix (Fig. 2*b*) in which proteoglycan granules are visible at EM level (Rufai et al. 1996). At the attachment of the rat Achilles tendon, the cells have a small Golgi apparatus, but abundant rough endoplasmic reticulum and numerous glycogen granules that often surround lipid droplets (Rufai et al. 1996). There may be fewer cells in the calcified zone, presumably a consequence of the reduced rate of diffusion and the subsequent cell death. In contrast to the junction between uncalcified and calcified fibrocartilage, that between calcified fibrocartilage and bone is highly irregular (Fig. 2*b*). The complex interlocking of tendon and bone is likely to be a major factor in securing their attachment. However, Clark & Stechschulte (1998) also presented evidence in an SEM study of the rabbit quadriceps tendon that the collagen fibres penetrate into the bony lamellae themselves.

Considerable data have accumulated on the immunohistochemical composition of enthesial fibrocartilage and to a lesser extent on the associated sesamoid and periosteal fibrocartilages as well. The classical fibrous collagens (types I, II and III) are well documented (Ralphs et al. 1991, 1992; Rufai et al. 1992; Kumagai et al. 1994*a*, *b*; Liu et al. 1996; Visconti et al. 1996; Waggett et al. 1998), but types V, VI, IX, X, XI and XIV collagens have also been reported (Niyibizi et al. 1995, 1996; Visconti et al. 1996; Waggett et al. 1998). Type I collagen is the typical collagen in the midsubstance of direct tendons/ligaments that is responsible for their high tensile strength. The type I fibrils must continue at least as far as the calcified cartilage- bone interface, because of the way the enthesis fibrocartilage develops (Fig. 4; Gao et al. 1996*b*). Our argument is as follows. Initially, hyaline cartilage alone is present at the enthesis and the tendon or ligament attaches to it (Fig. 4*a*). This hyaline cartilage is part of the original bone anlage that escapes erosion during the early stages of endochondral ossification (Ralphs et al. 1992; Rufai et al. 1995). However, as growth continues, the cartilage is eroded from the bone side and replaced by enthesis fibrocartilage on the tendon/ligament side (Fig. 4*b*, *c*; Gao et al. 1996 *b*). This means that the enthesis is effectively a 'growth plate', where cartilage destruction and formation are balanced on the bone and tendon/ligament side. The key point is that

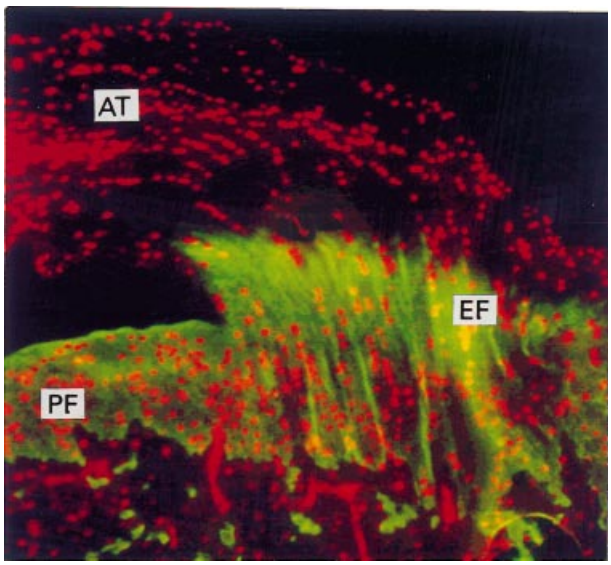


Fig. 5. Type II collagen immunohistochemical labelling (green) with antibody CIICI in the enthesis (EF) and periosteal (PF) fibrocartilages of the rat Achilles tendon (AT). The nuclei have been counterstained red with propidium iodide. Confocal laser scanning microscopy of a sagittal section from a 3-mo-old rat, ×80.

enthesis fibrocartilage only develops *within* the tendon or ligament. It does so by metaplasia of tendon or ligament cells and these of course are arranged in rows, separated by parallel, type I-containing collagen fibrils. Inevitably therefore, type I collagen fibrils must continue at least as far as the bony interface. The deep part of the fibrocartilage at an enthesis only becomes calcified as growth slows down and thus tidemarks are always most typical of adult animals. It follows therefore that collagen fibrils must be continuous across them. The metaplastic origin of enthesis fibrocartilage explains how it can reappear at an adult enthesis following the surgical reattachment of a tendon or ligament, even though endochondral ossification has been completed (Jones et al. 1987; Schiavone Panni et al. 1993). Intriguingly, both fibrocartilage formation in a reattached tendon and enhanced biomechanical properties of the attachment site can both be accelerated by treatment with BMP12 (Hattersley et al. 1998).

Type II collagen is the typical collagen of cartilage and that present at entheses is initially present in the hyaline cartilage of the bone anlagen. However, as the original cartilage remnant is eroded, the type II collagen that characterises adult entheses (Fig. 5) develops around the metaplastic fibrocartilage cells (Gao et al. 1996*b*; Messner, 1998). Type III collagen probably plays a role in controlling fibril diameter and forms heterotypic fibrils with types I and V collagen (Birk & Mayne, 1997; Waggett et al. 1998). Type VI collagen has been found in the mid Achilles tendon and in the enthesial, sesamoid and periosteal fibrocartilages of its insertion (Waggett et al. 1998). Its pericellular distribution in all fibrocartilages contrasts with its more general location throughout the ECM of the mid tendon and suggests different matrix binding functions. Type X collagen has recently been located immunohistochemically at the attachment of the rat Achilles tendon and the femoral attachment of the bovine medial collateral ligament (Niyibizi et al. 1996; Fujioka et al. 1997, 1998). It is produced by fibrocartilage cells near the tidemark and may prevent the spread of calcification into the tendon and maintain the interface between calcified and uncalcified tissues. Although Niyibizi et al. (1996) and Fujioka et al. (1997, 1998) emphasised that type X collagen persists throughout maturity at the enthesis and its expression is not transient as in epiphysial plates, it is still important to recognise that enthesial fibrocartilage *does* act as a mini growth plate at tendon/ligament insertions (Gao et al. 1996*b*). During the period of active growth, the fibrocartilage is eroded on the bone side and replaced by metaplastic fibrocartilage developing within the tendon or ligament.

A number of proteoglycans and their mRNAs have also been detected in enthesial fibrocartilage by immunohistochemistry, Western blotting and RT-PCR analyses (Waggett et al. 1998). They include the small proteoglycans decorin, fibromodulin and lumican that may be important in regulating collagen fibril formation and/or increasing their tensile strength (Vogel et al. 1984; Hedbom & Heinegård, 1989; Danielson et al. 1997; Pins et al. 1997), biglycan whose function is unclear and the large proteoglycans aggrecan and versican. Aggrecan enables the insertional fibrocartilages to resist compression and versican is the large PG characteristic of direct tendons.

### *Mechanical role of enthesis fibrocartilage*

In understanding the mechanical significance of enthesis fibrocartilage, it is helpful to compare a tendon that attaches to an epiphysis (e.g. supraspinatus—which attaches to the greater tuberosity of the humerus) with one that attaches to the mid diaphysis (e.g. deltoid, which attaches to a tuberosity on the shaft of the humerus). As the shoulder joint is abducted through 90°, there is a large change in angle between the long axis of the tendon of supraspinatus and the humerus, but very little change

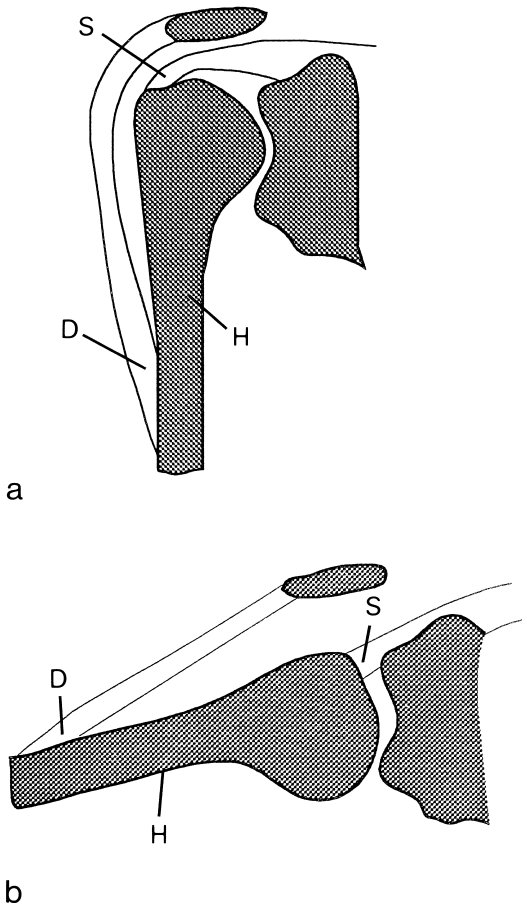


Fig. 6. Diagrammatic representation of why epiphyseal tendons have a greater risk of wear and tear at their entheses than do diaphyseal tendons. (*a*) The attachments of the tendons of deltoid (D) and supraspinatus (S) to the humerus (H) when the arm is adducted. (*b*) The same attachments when the arm is abducted through 90°. Note that there is little change in the angle at which the tendon of deltoid meets the humerus, but a pronounced change in angle for the tendon of supraspinatus.

in angle between the tendon of deltoid and the bone (Fig. 6; Benjamin et al. 1986). This probably means that there is an increased risk of wear and tear at the attachment of supraspinatus. It is commonly suggested therefore that the primary role of the enthesis fibrocartilage is to dissipate stress concentration at the bony interface (Benjamin et al. 1986; Woo et al. 1988). By promoting a gradual bending of collagen fibres (Fig. 2*c*), the uncalcified fibrocartilage acts like a rubber grommet on an electrical plug, protecting the tendon from compression, and the calcified fibrocartilage protects the bone from excessive shear (Schneider, 1956). Thus collectively, the zones of calcified and uncalcified fibrocartilage form a 2-layered defence system (Schneider, 1956). As ligaments are generally attached close to synovial joints, and as most tendons are attached just beyond the joint on which they principally act (so that their speed of action is maximised; Jones, 1941), it follows that most entheses are fibrocartilaginous.

There is a good correlation between the quantity of uncalcified fibrocartilage at an enthesis and the extent of movement that occurs between tendon/ligament and bone. At the insertions of the quadriceps and patellar tendons, there is approximately a 30° change in angle between tendon and bone during flexion and extension of the knee, but virtually no change in angle at the origin of the patellar tendon (Evans et al. 1990). There is significantly more fibrocartilage at the 2 tendon insertion sites than at the origin of the patellar tendon. Similarly, there is more fibrocartilage at the horns of the more mobile lateral menisci of the knee joint than the medial menisci (Benjamin et al. 1991) and a greater quantity of fibrocartilage at the insertion of biceps than at brachialis or triceps (Benjamin et al. 1992*b*). Although biceps, triceps and brachialis are all involved in flexion or extension of the elbow joint, biceps alone acts as a supinator and thus has a distinctive triplanar motion at its insertion site. All these regional variations in the quantity of uncalcified fibrocartilage at different entheses suggest that movement is the mechanical stimulus that triggers the metaplasia of fibroblasts to fibrocartilage cells. This is important to bear in mind in the design of rehabilitation programmes for patients who have undergone the surgical reattachment of a tendon or ligament. Even though the zone of uncalcified fibrocartilage takes much of the collagen fibre bending slightly away from the bone, it is still significant that the tidemark in a healthy tendon/ligament is relatively straight with no jagged edges protruding from the bone that could damage the tendon or ligament as it moves.

The thickness of the zone of calcified fibrocartilage and the extent of the interface that it provides for the bone may be related to the physiological strength and loading of the tendon or ligament (Gao & Messner, 1996; Inoue et al. 1998*a*). Gao & Messner (1996) have suggested that the shape and surface area of the calcified fibrocartilage-bone interface at ligament insertions is determined by the tensile loads to which a ligament is subjected around puberty, but the thickness of its subchondral plate may respond to loads beyond that time and reflect motion at the hard-soft tissue interface. This is in line with the earlier suggestion of Evans et al. (1991) that differences in the thickness of the subchondral plate at entheses relate to differences in their tensile loading. Virtually no attention has been paid to the bone at entheses, although Inoue et al. (1998*b*) have made a useful attempt to relate trabecular orientation at the in-

sertion of the canine patellar tendon with the direction of tensile loading in the tendon itself.

Tendons are not entirely inextensible cables that directly transfer the length change or force of a contracting muscle to a bone, but are capable of stretching and returning to their original length (Alexander, 1984). This property of elastic extensibility (i.e. tendon 'compliance') is perhaps counter-intuitive at first sight, for it is obvious that tendons simply cannot be allowed to stretch too much if they are to transfer muscle pull to bone. However, an ability to stretch and recoil up to 8 % without damage enables them to act as springs that transiently store strain energy and thus save on substantial quantities of metabolic muscular energy (Alexander, 1984). If tendons stretch, they must also narrow, and where they narrow, they may be more vulnerable to damage. It is intriguing to note therefore that Knese & Biermann (1958) suggested that enthesis fibrocartilage could act as a 'stretching brake' that prevents a tendon or ligament from narrowing at the point where it enters the bone—a region of stress concentration. This would complement the marked increase in the cross sectional area that many tendons/ligaments exhibit as they approach the bone. Differences in tendon compliance therefore may be related to why some tendons have more fibrocartilaginous entheses than others, even though the range of movement at the bone is similar. It may also be that fibrocartilage in wrap-around tendons reduces the risk of tendon narrowing at its vulnerable points of contact with bone. Any narrowing would increase the compression to which the tendon is subject as explained above.

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