Entheses: tendon and ligament attachment sites

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The current brief review focuses on certain issues relating to form–function relationships that are evident at tendon or ligament attachment sites (entheses). It evaluates the development of entheses (both fibrocartilaginous and fibrous) and highlights again an issue largely ignored for decades – i.e. how entheses attached to the metaphyses of long bones manage to keep the same relative position as the bones grow in length. Attention is drawn to the manner in which enthesis fibrocartilage prevents direct cell–cell communication between osteocytes and tendon/ligament cells and how (in a healthy enthesis) it presents a physical barrier separating the blood supply of bone from that of tendon/ligament. The possibility that the thoracolumbar fascia, with its multitude of muscular associations and numerous sites of ligamentous attachment could increase stress concentration at entheses is raised, the structure and development of enthesophytes (bony spurs) is reviewed as is the concept of a synovio-entheseal complex (SEC). How these functional anatomical units (SECs) could trigger pain and inflammation in athletes is briefly discussed.

An enthesis is the site of attachment of a tendon, ligament or joint capsule to the skeleton (Fig. 1). Its clinical significance is largely threefold – (a) it is a common region for overuse injuries; (b) it is targeted in rheumatic diseases known collectively as the seronegative spondyloarthropathies – which include ankylosing spondylitis and psoriatic arthritis; (c) it needs to be reconstituted when a tendon or ligament is reattached to a bone at surgery – e.g. in an anterior cruciate ligament reconstruction or a tendon transfer procedure. In addition, entheses have been of long interest to anthropologists and archeologists, for the markings left on dried bones by tendons and ligaments, or the influence of muscle pull on overall bone shape, have been interpreted by some authors as indicators of the type and/or extent of physical activity or whether an individual was right or left handed (Dutour, 1986; Drapeau, 2008).

The current article focuses on aspects of form–function relationships of entheses manifest at the tissue and organ level and seeks to complement rather than duplicate other recent reviews on entheses by the authors and their colleagues (Benjamin & McGonagle, 2001; Benjamin et al., 2002, 2008a, b; Milz et al., 2005; Shaw & Benjamin, 2007). Thus, the review does not attempt to deal in an exhaustiv way with all threads of the topic that might be suggested by its title. It focuses instead on developmental matters, the relationship between tendon and ligament entheses and fascia, the “barrier” characteristics of enthesis fibrocartilage at hard–soft tissue interfaces, the concept of a synovio-entheseal complex (SEC) and the structure, development and significance of enthesophytes (bony spurs at attachment sites).

Enthesis development

The story of enthesis development and of enthesis fibrocartilage differentiation in particular is an excellent illustration of how entheses can to a large extent, be regarded as self-designing systems where morphology is dictated by the influences of mechanical load. It is a clear example of how function dictates structure. A study of enthesis development helps us to understand how mechanical influences can account for differences in the quantity of fibrocartilage at different entheses (Evans et al., 1990; Benjamin et al., 1991, 1992), the regional distribution of fibrocartilage within an attachment site and the site of development of bony spurs (Benjamin et al., 2008a, b; McGonagle et al., 2008). Intriguingly, one of the great pioneers of enthesis biology, Schneider (1956) commented on how the structure of the biceps brachii enthesis differed in a person who had spent a lifetime cleaning windows (hence with a pronated forearm) compared with a farm hand who
had spent his time milking cows (with a supinated forearm)!

Our understanding of the differentiation of fibrocartilage during enthesis development is aided by the immunohistochemical study of Gao et al. (1996) on the femoral attachment of the medial collateral ligament (MCL) of the rat knee joint. In the fetus or newborn rat, the tendon/ligament initially attaches to the hyaline cartilage that forms the anlagen for the future bone. As ossification occurs and bone replaces hyaline cartilage, the cartilage at the attachment site initially escapes erosion to leave a cartilage disc at the attachment site. However, this plug of hyaline cartilage is eventually completely resorbed and replaced by fibrocartilage (Fig. 2). The resorption and replacement occur hand in hand and a key point is that the fibrocartilage develops by metaplasia in the tendon or ligament. Thus, cells that were initially differentiating into fibroblasts now change phenotype and become fibrocartilage cells. If the tendon/ligament fibroblasts were arranged in longitudinal rows between parallel collagen fibers at the enthesis, then the fibrocartilage cells become arranged likewise (Fig. 1). It seems highly probable that the signal for metaplasia is mechanical loading and in particular, elevated levels of compression and/or shear – in-line with general principles relating to the development of fibrocartilage elsewhere (Benjamin & Ralphs, 1998). Thus, in the rat knee joint, the enthesis fibrocartilage of the MCL replaces the original hyaline cartilage rudiment between 30 and 45 days post-partum (Gao et al., 1996) – i.e. after a period of physical activity and at a time corresponding to an increase in the mechanical strength of the ligament (Booth & Tipton, 1970; Tipton et al., 1978). Further evidence supporting the importance of mechanical loading for enthesis fibrocartilage development comes from the experimental work of (Thomopoulos et al., 2007) on the supraspinatus enthesis of the mouse. When the left shoulders of newborn mice were paralyzed by intramuscular injections of botulinum A toxin, fibrocartilage development was strikingly delayed compared with the contralateral shoulder, which received a saline injection alone. This work contrasts strikingly with the findings of Zumwalt (2006) who investigated the relationship between enthesis morphology of six different well-defined tendons, and corresponding muscle action/size in adult sheep. Her interest largely related to attempts by archeologists to gain an insight into likely activity levels from skeletal remains. Thus, it must be recognized that her evaluations of enthesis morphology were entirely restricted to the surface features of adult macerated bones. Nevertheless, it is worth noting that “endurance-trained sheep” (exercised for 90 days) did not have a macroscopic bone morphology at attachment sites that differed from

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**Fig. 1.** The olecranon enthesis of triceps brachii in man. As the tendon approaches the bone (B), it becomes fibrocartilaginous. A broader zone of uncalcified fibrocartilage (UF) is separated from a thinner region of calcified fibrocartilage (CF) by a tidemark (T). This represents the outer limit of calcification and is thus the hard–soft (i.e. mechanical) boundary of the attachment site. Its straight characteristic contrasts with the irregular interface (*) of the true tissue boundary between bone and tendon. Note that the cells in the zone of uncalcified fibrocartilage (arrows) are arranged in longitudinal rows between parallel collagen fibers (C) and that in this non-pathological specimen, there are no blood vessels visible in the fibrocartilage zones. Masson’s trichrome. Scale bar = 100 μm.

**Fig. 2.** A diagrammatic representation of the development of fibrocartilage at the femoral attachment of the medial collateral ligament of the rat knee joint, based on the work of Gao et al. (1996). (a) Initially, the tendon or ligament [characterized by differentiating fibroblasts (F)] attaches to the hyaline cartilage (HC) that preceded the bone rudiment. (b) As ossification ensues, the hyaline cartilage is eroded, but fibrocartilage (FC) appears in the tendon or ligament because of metaplasia of the fibroblasts. (c) The metaplasia is probably driven by mechanical stimuli associated with movement of the tendon or ligament relative to the bone (B) at the insertion site. (d) Eventually all the original cartilage rudiment is resorbed, but further fibrocartilage forms in the tendon or ligament by continuing metaplasia.
that of controls. Whether this reflects the type of muscle fiber activity promoted by endurance training or the use of adult rather than juvenile animals is unclear. It is also uncertain whether endurance training influences enthesis structure at a cell, tissue or molecular level. Although the effects of endurance training on enthesis structure are unknown, a greater cross-sectional area of the Achilles tendon in distance runners than non-runners has been noted (Magnusson & Kjaer, 2003). The same authors stated that the increase in cross-sectional area affected the distal part of the tendon, but it was unclear whether this embraces the precise site of tendon attachment to the calcaneus (Magnusson & Kjaer, 2003). It would thus be interesting to know if the “footprint” of the tendon is correspondingly expanded in runners. If so, this suggests appositional growth of the attachment site – implying fibrillogenesis around the circumference of the “trained enthesis” in order to dissipate stress concentration in-line with the increased loading on the tendon. However, if the footprint is not increased, stress concentration per unit area must be greater and this could have a bearing on the incidence of insertional tendinopathies. Such considerations are entirely conjectural, but worthy of further investigation in a suitable animal model.

There is an intriguing issue concerning the development of entheses that attach to the shafts of long bones that also highlights the importance of mechanical loading. Such tendons or ligaments need to migrate along a bone as it grows, in order that they can maintain the same relative position with respect to the growth plate. A number of authors have addressed this issue over the years, but perhaps the most important contributions are those of Dorfl (1980a, b). As Dorfl points out, the migration reflects the fact that interstitial growth does not contribute to the elongation of diaphyses – which can only grow in length by the activity of the epiphyseal growth plate. Thus, if a tendon/ligament does not migrate at a rate matching the overall growth in length of the long bone to which it is attached, it will eventually be attached nearer to the middle of the shaft by adulthood (Dorfl, 1980a). The necessary migration can be promoted by an attachment of the growing tendon/ligament to the periosteum rather than to the bone itself. As the periosteum is stretched by the growth in length of the long bone and/or by muscular traction, the entheses are “dragged” with it (Dorfl, 1980a). The rate of migration depends on the position of the enthesis relative to the growth plate and to the “neutral center.” LaCroix (1949) defines this as the place at which the periosteum is pulled equally in two opposite directions by the activity of the proximal- and distal-growth plates. The location of the neutral center varies from bone to bone, according to the proportional contribution to growth in length attributable to the epiphyseal growth plates at either end of the long bone. The farther away an enthesis is from the neutral center, the greater the rate of migration. The periosteum drags the enthesis with it and is itself pulled by the epiphyses as these are pushed apart by growth plate activity (Dorfl, 1980a). Intriguingly Dorfl argues that the details of the mechanism of migration vary and depend on whether the tendon/ligament is attaching to a resorptive surface, an osteogenic surface or a surface that is both resorptive and osteogenic. Thus the tendon/ligament does not necessarily have to slide over the bone surface – its migration can be facilitated by interstitial growth of the enthesis itself if the developing enthesis is characterized by an osteogenic zone (Dorfl, 1980a). Dorfl hypothesizes that the collagen fibers lengthen at the insertion site where an osteogenic zone is present, so that the attachment itself is always maintained. Where the attachment is to an absorptive surface, fibrillogenesis occurs and there is possibly also a shortening of existing fibers (presumably reflecting matrix metalloproteinase activity) that helps to maintain a continuous bony attachment during growth. The molecular basis of such events is completely unexplored.

The tension within the collagen fibers that facilitates migration could be regarded as producing defined traction lines directing enthesis migration in a macroscopic equivalent of traction lines directing cell migration in a culture dish in vitro. It is also a good example of a tensegrity system operating at the tissue level. Interestingly, the experimental studies of Dorfl (1980b) show that if the growth plates are prevented from functioning properly and thus tension does not develop in the periosteum, the entheses do not migrate. He confirmed this by inserting staples into rabbit long bone to arrest growth plate activity. Without normal bone lengthening, the periosteum is not stretched, and thus the periosteum cannot drag any entheses with it (Dorfl, 1980b). Grant et al. (1980) also has recognized the importance of tension developing in the periosteum as a result of growth plate activity. He referred to the periosteum at such locations as an elastic sleeve and envisaged soft tissues (muscles, tendons, ligaments) attaching to it as being like hitchhikers carried along an expanding periosteum (Grant et al., 1980).

**Fascia and entheses**

The importance of fascial expansions of entheses to adjacent structures (including other entheses) as a mechanism for stress dissipation has been emphasized in recent reviews (Benjamin et al., 2008a, b). Here we focus attention on the converse point of

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**References**


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**Notes**

- In the cited works, the terms “enthesis” and “insertion” are used interchangeably, with the latter term being more common in modern literature. The term “enthesis” is derived from the Greek “enthesis,” meaning “attachment.”
- The definition of the “neutral center” is crucial for understanding the rate of enthesis migration, as it determines the mechanical forces acting on the enthesis.
- The role of matrix metalloproteinases (MMPs) in enthesis remodeling and integration with bone is an important area of research, as MMPs are responsible for the breakdown of extracellular matrix proteins during bone remodelling and enthesis formation.

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**Figures**

- Figure 1: A schematic diagram illustrating the attachment of a tendon to bone, showing the principle of enthesis development.
- Figure 2: A micrograph of an enthesis showing fibrillogenesis and matrix deposition.
whether fascial connections may actually increase the stress levels to which entheses are exposed. Consider the thoracolumbar fascia (TLF). This very extensive and complex collection of sheets of dense connective tissue is arranged at various depths in the thoracic and lumbar regions of the spine (Bogduk & Macintosh, 1984; DeRosa & Porterfield, 2007). It provides an important surface for muscle attachment and its extensive nature means that seemingly disparate muscles of the trunk and extremities are mechanically linked to each other by virtue of their common fascial connections (Vleeming et al., 1995; DeRosa & Porterfield, 2007). Thus, the TLF effectively couples together gluteus maximus, latissimus dorsi, erector spinae, multifidus, quadratus lumborum, the rhomboids, biceps femoris and the flat muscles of the abdominal wall! This is an impressive diversity of muscles spanning the trunk, pelvis and extremities. As the fascia also attaches firmly to many ligaments (each with its own enthesis), it means that stress concentration at an individual bone–ligament junction can be influenced by events some considerable distance away. For example, stress concentration at a facet joint capsule could theoretically be influenced by, e.g. multifidus tone, for the TLF fuses with the supraspinous ligaments which in turn are continuous with the interspinous ligaments anchoring to the facet joint capsules (Willard, 2007). Such an interspinous–supraspinous–thoracolumbar ligament complex creates a central support system for the lumbar spine (Willard, 2007).

By a similar reasoning, many muscles can generate force that is transferred to the sacroiliac joint (SIJ) and its entheses via the TLF – potentially increasing stress concentration at these sites. It should be noted that the TLF attaches to the ligamentous stocking that surrounds the lumbar spine and expands inferiorly to form a strong and delicate posterior capsule for the SIJ (Willard, 2007). Evidently, muscle contraction stabilizes the lumbar spinal region in a way that ligamentous restraints alone cannot (DeRosa & Porterfield, 2007). Thus, van Wingerden et al. (2004) have shown that isometric contractions of biceps femoris, gluteus maximus or erector spinae can increase the stiffness of the SIJ. They suggested that the muscle-induced stiffness reduced the levels of shear in the SIJ in preparation for load transfer from the spine to the legs. If the suggestion is correct, it not only means that shear is reduced in the synovial part of the joint, but also in the fibrous part – i.e. at the entheses of the interosseous ligament. Nevertheless, the tensile loading of attachment sites is likely to be increased and thus it seems possible to argue that muscle tone could both increase and decrease aspects of stress concentration at SIJ joint entheses.

Francois et al. (2000) have cautioned that enthesitis is not the sole contributory factor to SIJ joint disease in ankylosing spondylitis but that synovitis and subchondral bone marrow changes may offer a better explanation for the joint destruction that occurs in this disease. Nevertheless, they recognize that enthesitis is a feature and thus the influence of muscle tone and myofascial stiffness on the SIJ and its ligaments merits further consideration. In this context, it should be noted that Masi et al. (2005) have drawn attention to the forgotten “bowstring sign” of Jacques Forestier in early ankylosing spondylitis. Such patients have firm, contracted dorso-lumbar muscles on the concave side when the patient flexes his/her spine laterally. This is not a feature of normal individuals, but the observation is not widely known by rheumatologists today.

Enthesis fibrocartilage as a barrier to direct cellular communication between tenocytes and osteocytes

It is well known that osteocytes have numerous elongated processes that extend into canaliculi, permeating the bone matrix and communicating with each other via gap junctions. Equally, gap junctional communication is a feature of tendons, for confocal microscopy demonstrates that these cells also have long, delicate processes that contact those of neighboring cells (McNeilly et al., 1996). Gap junctions are present both between tendon/ligament cells within the same longitudinal row and between cells in adjacent rows (McNeilly et al., 1996) and their location is shown diagrammatically in Fig. 3. Critically, however, the cells of enthesis fibrocartilage do not express connexins (Ralphs et al., 1998; Fig. 3) and thus as in hyaline cartilage, intercellular communication must be indirect – via cell–matrix interactions. This creates a barrier to direct cell–cell communication between tendon/ligament and bone, complementing the vascular barrier stemming from the lack of blood vessels in the enthesis fibrocartilage of a healthy attachment (Fig. 1). The significance of this is unclear but it may be related to preventing bone tissue growing into tendons or ligaments. This is supported by the observation that bony spurs typically develop in the most fibrous regions of fibrocartilaginous entheses (Benjamin et al., 2008a, b).

Synovio-entheseal complexes

Benjamin & McGonagle (2001) coined the term “enthesis organ” to capture the idea that there is more to an enthesis than simply the attachment site itself. Many tendons or ligaments attach to bone at the bottom of a shallow pit or adjacent to a slightly elevated region of bone (e.g. a tuberosity) so that there is the potential for a degree of mechanical...
leverage between the tendon/ligament and the bone immediately adjacent to the attachment. This helps to dissipate stress concentration away from the enthesis itself. A common component of many enthesis organs is synovium. This may line a subtendinous bursa, form a tendon sheath that extends close to the attachment site itself or be part of an adjacent synovial joint. Thus a region vulnerable to mechanical damage (the enthesis), that is essentially anti-inflammatory and poorly vascularized is juxtaposed to a rather different tissue (synovium) that in contrast is pro-inflammatory and highly vascular. In order to emphasize the importance of recognizing this anatomical proximity, we have coined the term synovio-entheseal complex (McGonagle et al., 2007) and documented examples of SECs in a follow-up paper (Benjamin & McGonagle, 2007). The SECs associated with the insertions of the subscapularis tendon on the lesser tuberosity of the humerus and the Achilles tendon on the calcaneus are illustrated in Figs 4 and 5.

We have argued that synovial membranes near entheses “walk an immunological tightrope” in so much as tissue breakdown products resulting from wear and tear at an attachment site could trigger an inflammatory reaction in the adjacent synovium (McGonagle et al., 2007). Such a concept is particularly relevant to the seronegative spondyloarthropathies (SpA) where enthesitis and synovitis are often viewed as independent pathologies. It suggests the possibility that bursitis could lead to enthesitis and vice versa – a suggestion made earlier by Rufai et al. (1995). Thus the term “synovio-entheseal complex” is an attempt to increase awareness that (a) enthesitis and synovitis may not necessarily be independent pathologies (b) degenerative changes at an enthesis could trigger inflammation in a synovial membrane that is not part of a synovial joint.
Bony spurs (enthesophytes) are common features of attachment sites. They include the syndesmophytes that develop in the annulus fibrosus (and which by their growth can lead eventually to spinal ankylosis in SpA patients) and bony spurs that grow at or near numerous other entheses [particularly the Achilles tendon (Fig. 5) and plantar fascia]. They are obviously closely related to osteophytes that develop at the periphery of synovial joints in association with degenerate articular cartilage in patients with osteoarthritis. Indeed it has been suggested that the development of both types of spurs is due to the fact that some people are intrinsic “bone formers” (Rogers et al., 1997). They even suggest that differences in the propensity for spur formation between individuals could contribute to the mixed clinical outcomes that certain treatment protocols may produce. Intriguingly, Menz et al. (2008) also provide evidence supporting a link between osteoarthritis and the formation of plantar calcaneal enthesophytes. In our studies we have noted that young normal subjects often have small Achilles tendon spurs (McGonagle et al., 2008).

We have recently analyzed the structure of enthesophytes of different sizes, at a wide variety of attachment sites in order to try to piece together an account of how they could develop (Benjamin et al., 2008a, b). It seems that in man at least, their development can embrace a number of methods of ossification – endochondral, intramembranous and chondroidal. Evidence of endochondral ossification is suggested by the presence of calcified cartilage remnants in the cores of some larger spurs. Curiously, however, signs of chondrocytic hypertrophy are far less striking than they are in the classic endochondral ossification that typifies the growth plate of a long bone. Although it is possible that marked hypertrophy does indeed occur in enthesophytes that form with age in man and has simply been missed because of its short duration, it is also worth considering that the absence of significant hypertrophy reflects a much slower rate of bone development in a spur compared with a growth plate. Whatever the explanation, it is certainly the case that enthesophytes usually develop at the edge of an enthesis – generally the most fibrous (and thus least cartilaginous) part of a fibrocartilaginous attachment site (Benjamin et al., 2008a, b). This observation is in line with the widespread view that enthesophytes are generally traction spurs. Nevertheless, we ourselves have argued that plantar fascial spurs cannot be traction spurs, for they must lie on the surface of the plantar fascia rather than within it (Kumai & Benjamin, 2002). We have suggested that they develop in response to degenerative changes at the enthesis. Our histological observations on the location of plantar fascial spurs are supported and extended by the radiological studies of Abreu et al. (2003). According to these authors, heel spurs developing on the plantar surface of the calcaneus can arise at several different locations – notably the attachments of local intrinsic muscles, but rarely in the plantar fascia itself. More recently, Li and Muehleman (2007) have also expressed the view, based on their radiological, gross anatomical and

**Fig. 5.** The synovio-entheseal complex at the insertion of the human Achilles tendon (AT) onto the calcaneus (C). Note that the enthesis (E) lies adjacent to a bursa (B) into which the synovial-covered tip of a fat pad (FP) protrudes. There is a prominent spur in the distal part of the enthesis. Toluidine blue. Scale bar = 4 mm.
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histological studies, that plantar spurs do not develop in response to traction. An important point made by these authors is that the trabecular organization of the spurs is more suggestive of compressive forces acting on the spur than tensile loading along its long axis. The importance of compression in the development of plantar heel spurs is further supported by the recent work of Menz et al. (2008)—who found that patients with such spurs are more likely to be obese than those without.

Perspectives

A sound understanding of form–function relationships of entheses underpins any appreciation of what may be happening in pathological conditions—whether the enthesopathies are associated with the development of overuse injuries or with the spondyloarthritides. In relationship to overuse injuries, we have noted that even normal attachments are prone to microdamage and microscopic inflammation. It appears that overuse exaggerates this response and leads to clinically manifesting disease. Following on from this, it would seem that overuse injuries including bursitis are likely to be (at least in part) enthesis organ damage manifesting as adjacent synovitis.

Key words: insertion sites, enthesopathy, development, fibrocartilage, fascia.

References


