CHAPTER 1

DEFINITION AND FUNCTION OF THE ENTHESIS

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The enthesis, or tendon-to-bone insertion site, is defined as the area where a tendon, ligament, or joint capsule inserts into the bone and acts to transmit the tensile load from soft tissues to bone. Entheses are important parts of the musculoskeletal system, organizing its various components, such as bones, muscles, tendons, and ligaments, into a functional organ system to work together. The distinct organization of that tendon/ligament to bone insertion sites is essential to the proper function of the respective muscular/skeletal structures. Mechanical damage to entheses may account for the surgical challenges associated with the need for the reconstruction of damaged insertion sites.

Chronic inflammation as a result of a mechanical overload or a systemic disease may also lead to a longstanding need for treatment. The goal of this chapter is to describe the anatomy and histology of the enthesis and its normal function in the human body (**Figure 1.1**).

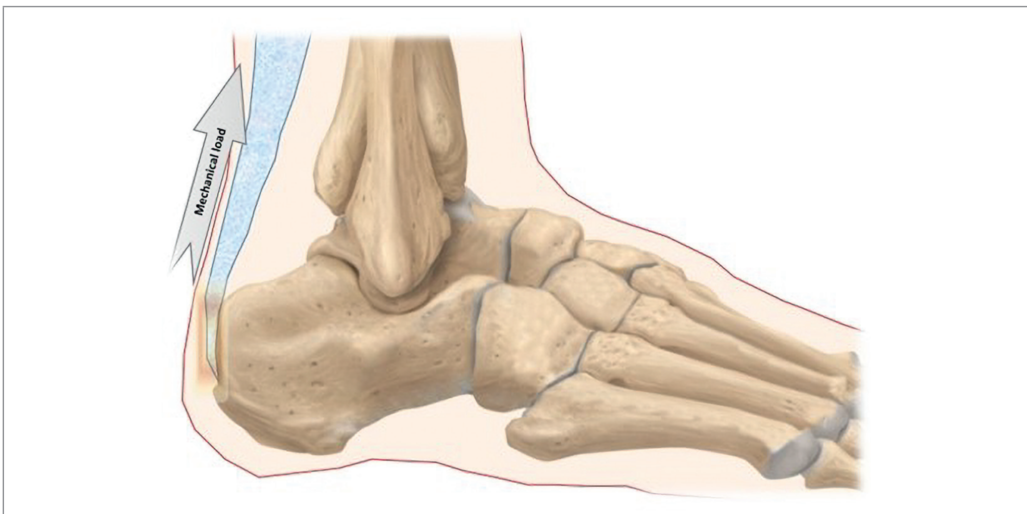


Figure 1.1 An enthesis, using the example of the Achilles tendon.

DEFINITIONS AND EVOLUTION OF THE ENTHESIS CONCEPT

The term "enthetic", derived from the ancient Greek word "enthetikos", meaning "put in" or "placed on", was used in the nineteenth century to refer to diseases inoculated or implanted into the body from external sources, particularly infections.[1]

By the early twentieth century, the adjective had been transformed into a noun, "enthesis", which meant the insertion of metallic or other non-vital material to replace lost tissue or remedy a defect in the body. The term was not used as it is today until the 1960s-1970s, when it started to appear in the English-language scientific literature, referring to focal insertional abnormalities at sites of bony attachments to tendons, ligaments, fascia, muscles, or joint capsules.[2, 3] Initially, enthesitis was viewed as an exact point of the tendon-to-bone insertion site. Therefore, enthesopathies were viewed as focal, insertional disorders, mainly in the sense of a traumatic or micro-traumatic disease of insertions.

Ball[4] was probably the first to use the term "enthesopathy" extensively to describe the inflammatory changes of insertions in spondyloarthritis. Further works confirmed enthesitis to be common in spondyloarthritis. In 1995, a European League Against Rheumatism (EULAR) workshop recommended that enthesopathy be used to designate "any pathologic change of an enthesis," the inflammatory changes deserving the more precise term of enthesitis.[5] Further diagnostic developments, in particular, the introduction of magnetic resonance imaging (MRI) and ultrasound into the clinical practice, have revealed that enthesopathy encompasses pathologic changes extending to the adjacent bone and soft tissues.[6]

Since then, it has been argued that this entity should be rather considered an "enthesis organ," encompassing not only the enthesis merely as the insertion site or focal attachment, but also the fibrocartilage, bursa, fat pad, adjacent trabecular bone networks, and deeper fascia as parts of an "enthesis organ complex" that may dissipate stress concentration at the bony interface away from the attachment site itself.[7] Later on, the concept of an enthesis organ was purified with the description of the "synovio-entheseal complex",[8, 9] which refers to the relationship between the proinflammatory synovium and the avascular enthesis.

As the meeting point between two types of tissue (soft and hard) with contrasting physical properties, the enthesis is known to be a site of repetitive biomechanical load and a region of high concentration of mechanical stress, with effects not only on the bony attachment interface and the enthesis itself but also on these neighboring tissues.[2] Indeed, strain levels at tendon or ligament entheses can be up to 4 times those that occur in midsubstance. Stress concentration is further increased because the angle at which the soft and hard tissues meet (the "insertional angle") changes with joint movement.

The dynamic changes in this angle occurring with locomotion increase the risk that tendon or ligament collagen fibers will fray at the bony interface. High biomechanical stress at the enthesis may trigger an inflammatory cascade with cytokine production by monocytes and lymphocytes infiltrating the adjacent synovial tissue, resulting in an articular inflammatory response, and clinically leading to synovitis adjacent to attachment sites.

Because stress concentration is such an issue at attachment sites, the whole architecture of entheses is geared toward stress dissipation. High biomechanical stress often needs a functional adaptation in the neighboring structures that are closely related to the attachment site of a tendon, ligament, or joint capsule, which together with the enthesis itself serve to dissipate stress concentration at the soft-hard tissue interface.[9] For example, bone sclerosis or new bone formation at the insertion site might be considered such an adaptation.

Thus, this concept of a "synovio-entheseal complex" has shifted the traditional view of enthesopathies from being regarded as focal disorders of entheses, to multifocal problems, which affect a much wider area.[7, 9]

ANATOMY AND COMPOSITION

The enthesis belongs both to the inserted structure and to the bone to which it is attached. It becomes part of the bone organ but remains distinct from mature bone tissue.[3] As an enthesis is an interface where a tendon meets a bone, they are found in all tendon-to-bone insertions throughout the body.

There are over 640 muscles in the body, with some of them having more than two attachment sites. Nevertheless, it should also be recognized at the outset that not all muscles attach to bone by means of tendons and that not all tendons have entheses. Many muscles attach to relatively large areas of the skeleton by “fleshy” fibers, a few tendons that link one region of a muscle to another, and others that are simply present on the surface of a muscle as aponeuroses that enable one muscle to glide over another.

Furthermore, in certain powerful pennate muscles, there may be many small intramuscular tendons that attach it to the bone, rather than a single discrete tendon. Even where muscles attach to bone by fleshy fibers and thus lack tendons completely, skeletal muscle fibers still do not anchor directly to a bone; it is rather the fibrous connective tissue associated with the muscle that promotes the attachment.[10-13] Mimic muscles do not attach to the bone but to the skin, at least with one end. Altogether, the number of tendon attachment sites reaches about 1,300.

There are also over 200 bones connected to each other, with each joint having a joint capsule that attaches to bones and usually at least two ligaments to fortify the joint. This puts the combined number of attachment sites that could be named as entheses to over 2,000.

From the histological point of view, entheses may be broadly classified as one of two categorical units – fibrous and fibrocartilaginous, depending on tissue type present at the osteotendinous junction. Fibrocartilaginous entheses are present on the epiphyseal or apophyseal long bone ends (so mainly “periarticular” entheses). Fibrocartilaginous entheses typically attach tendons to small, localized regions of bone that lack a thick cortical layer and periosteum. This allows more precise limb movements about the joint and may potentially dissipate stress as the thin cortical shell deforms under loading. By contrast, fibrous entheses attach to long bone diaphysis (therefore being mainly extraarticular).[7]

Such entheses are typically associated with large, powerful muscle bodies, such as the quadriceps group and the deltoid muscle. Periosteal attachments dissipate stress over a large expanse of bone, limiting their ability to stretch. Alternative, anatomic classification divides the entheses to joint-related (hereinafter called “articular”) or extraarticular according to whether the enthesis lies internally or externally relative to the capsule of a synovial joint.

The two types correspond to the dual origin of bone. During organogenesis and further growth, bone develops within a pre-existing connective tissue, either within a cartilaginous primordium (cartilaginous tissue in its earliest recognizable stage of development), such as endochondral bone, or within fibrous tissue, such as membranous bone, for example, the calvaria.[3] Tendons and ligaments attached to a bone of chondral origin are first linked to the primordial (primal) cartilage. The inner part of the cartilage is progressively replaced by bone; nevertheless, some cartilage is left throughout the growth period at places of tendon or ligament insertion. That cartilage is eroded at the inner, bony side by endochondral ossification, but at the outer, tendinous or ligamentous side, primordial (premature) chondrocytes or metaplastic chondrocytes from the tendon or ligament multiply to keep a transitional fibrocartilage layer at the insertion.

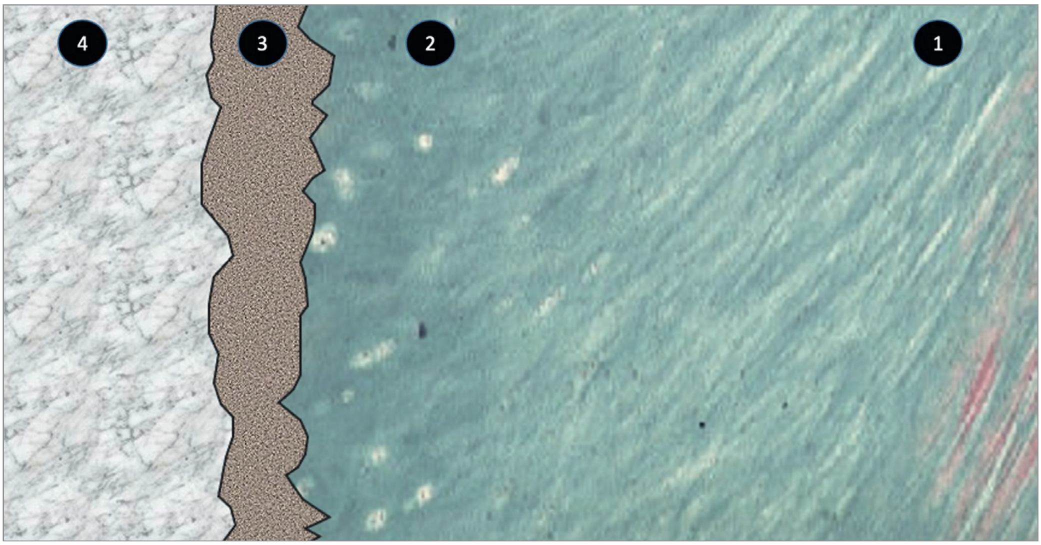


Figure 1.2 Four zones of a fibrocartilaginous enthesis (1: tendon, 2: uncalcified fibrocartilage, 3: calcified fibrocartilage, 4: bone).

The deeper area of the fibrocartilaginous enthesis is ossified and is firmly linked to the bone tissue by its irregular interlocking shape, possibly by an intermingling of the very end of tendinous fibers with the surface of bone collagen, and focally at least by a cement line.[3] Thus, in the adult, the fibrocartilaginous entheses have four components (Figure 1.2):

1. tendon with characteristic scattered longitudinally orientated fibroblasts within dense fibrous connective tissue, composed of linearly arrayed type I collagen fibers and proteoglycans, forming the tendon proper;
2. a zone of uncalcified fibrocartilage where the cell morphology changes to chondrocytes and the extracellular matrix contains proteoglycans (such as aggrecan) and multiple collagen types, with types II and III being the most prevalent;
3. a zone representing a mostly abrupt transition to calcified fibrocartilage, which is predominantly type II collagen, but there are also significant amounts of type X collagen as well as aggrecan. This zone serves to anchor tendon to bone, forming a highly irregular junction between collagen fibers and lamellae. Cartilage that anchors tendons during endochondral ossification remains and calcifies via metaplasia; thus, calcified fibrocartilage is the functional equivalent of collagenous fibers present in fibrous entheses that calcify within interstitial bone. The avascular calcification front, or tidemark, separates the zones of uncalcified and calcified fibrocartilage and serves as a boundary between soft and hard tissues;
4. bone proper, within which osteoblasts, osteocytes, and osteoclasts reside in a matrix of mineralized type I collagen.

Although the insertion site has classically been defined as containing these four zones, it is emphasized that the stratified tissue regions are compositionally distinct but structurally continuous. As described in subsequent sections, this controlled spatial distribution in matrix structure and composition is largely responsible for the functional grading necessary for minimizing stress concentrations between the connective tissue and bone.[10]

In decalcified sections, the boundary between uncalcified and calcified fibrocartilage is indicated by a faint “tidemark.” The uncalcified fibrocartilage zone creates a vascular and cellular barrier and helps reduce wear and tear by stress dissipation, as does the articular cartilage.

As the bone underlying the chondral enthesis has been deposited after chondroclastic removal of the cartilaginous primordium, collagen fibers of the fibrocartilage are unlikely to penetrate the bone tissue any deeper. Instead, calcified tendon fibers interdigitate among separate bone lamellar systems but do not merge with the collagen system of individual bone lamellae. At some places, such as at the tibial tuberosity or the vertebral ring apophysis, a secondary ossification center develops within the fibrocartilage at the distal end of the ligament.

Fibrocartilage is in general an intermediate tissue between dense connective tissue and cartilage. There is some similarity between a fibrocartilaginous enthesis and the way hyaline articular cartilage is fixed to the underlying bone. The deeper zone of the cartilage is calcified; the bone-cartilage boundary may be irregular and often presents a cement line. Thus, the same sequence of uncalcified cartilage, calcified cartilage, and bone is observed as at a fibrocartilaginous enthesis.[3]

In contrast to fibrocartilaginous entheses, fibrous entheses have enjoyed less attention, even though they are associated with some of the largest and most powerful muscles in the body. Unlike endochondral bone, membranous bone during ontogeny is not formed by replacing a previously existing structure, but rather by a direct transformation of fibrous tissue into bone. Fibroblasts or mesenchymal stem cells differentiate in osteoblasts between existing type I collagen bundles. As a consequence, the tendinous or ligamentous collagen fibers are not replaced by bone but are incorporated as “fleshy fibers” or Sharpey’s fibers – the term used by histologists to designate collagen bundles from periosteum, tendon, or ligament penetrating bone for quite a distance into so-called bundle bone – attaching either directly to bone or indirectly via the periosteum.

When serving to attach periosteum, they are rather scanty; in the case of tendon or ligament attachment, they are more densely packed, and the bone formed around them takes a striated aspect, deserving the name of bundle bone. Progressively, bundle bone is replaced by mature lamellar bone. In places, a cement line can be observed at the interface between bundle bone and lamellar bone. Fibrous entheses that lack tendons typically insert dense connective tissue fibers directly into the periosteum, equally allowing stress transmission over a large area. With age, many periosteal fibrous entheses become bony attachments or become ossified (turned to a bone) as the periosteum disintegrates over time.

The distinction between enthesis type and location corresponds also to the location of a new bone formation (mainly as a consequence of chronic inflammation), either intramembranous or endochondral ossification.[11] Fibrous entheses rooted in thick layers of cortical bone ossify intramebranously (*e.g.*, periostitis), while those attaching to thin cortical layers are fibrocartilaginous, ossifying endochondrally or periarticularly (*e.g.*, leading to the formation of bony spurs, osteophytes, or syndesmophytes).

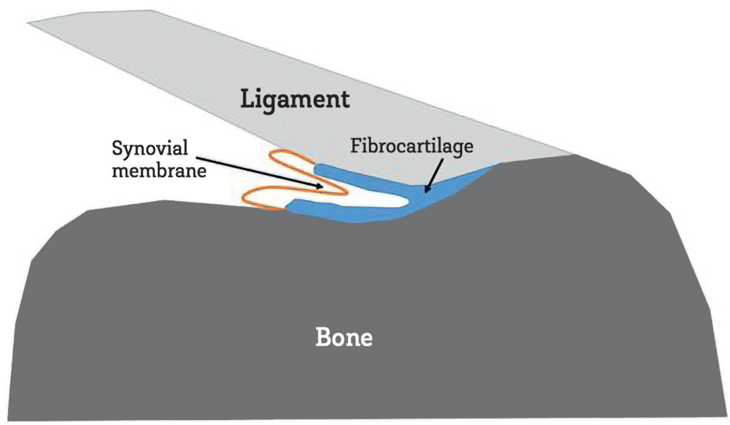
Over time, the concept of enthesis has been transformed into a concept of an "enthesis organ", composed of the enthesis insertion and adjacent tissues. An organ is a group of tissues that work in harmony to carry out a common function, and the enthesis organ works to aid locomotion and to minimize tissue damage.[12] While the insertion itself provides firm anchorage to the underlying bone, like the roots of a tree anchor it to the ground, several other tissues as well play an important role in the proper functioning of the enthesis. The following structures are referenced as the enthesis organ components:

- the underlying bone;
- the adjacent bone surfaces – insertions may run over bony prominences termed tuberosities. As a result, the tendon that is located well away from the attachment site proper is compressed against the adjacent bone during movement, thus limiting the stress at the actual insertion point. A variation on this is that entheses may arise from pits of depressions in the bone leading to bone stressing being spread over a wide area;
- the adjacent part of ligament or tendon, lined by fibrocartilage with the periosteal fibrocartilage. The cartilage lining the bone surface is termed the periosteal fibrocartilage and the one lining the under surface of the tendon or ligament is called the sesamoid fibrocartilage;
- soft tissues including the synovio-entheseal complex – an especially important component of the enthesis organ where bursal and other synovial cavity resident macrophages provide lubrication, nourishment, and metabolic requirements as well as micro-debris waste disposal in health;[13]
- adjacent supportive soft tissue, such as a fat pad or fascia. Fat is a liquid at body temperature and therefore is capable of acting as an additional shock absorber. Both adipose tissue and fascia carry blood vessels that supply the enthesis as well as nerve routs.

Given the multiple components of the enthesis organ, diseases associated with the enthesis organ may involve not only the insertion site itself, but the surrounding tissues such as bone, bursa, fat pads, ligaments, etc. The recognition that the enthesis is an organ helps to conceptualize why entheseal inflammation may be associated with diffuse extracapsular swelling in addition to synovitis and osteitis.[14]

In a cadaver study, Benjamin *et al.*[7] demonstrated that the concept of an "enthesis organ" can be applied to many (but not all) tendon and ligament attachments, as many entheses formed part of an enthesis organ. The composition and complexity of the enthesis organ was different, with some being simple, but others quite complex. The enthesis organ would usually comprise not only the enthesis itself, but also fibrocartilage and adjacent bursa(s) together with the bursal cavity and its associated synovium-covered fat pad(s) (**Figure 1.3**).

Fibrocartilage may include sesamoid fibrocartilage in the deep part of the tendon and periosteal fibrocartilage. Nevertheless, there may be some variations depending on the location and type of the enthesis and the adjacent structures. For example, an enthesis at the site of the extensor pollicis longus insertion (which is articular) is closely related to synovium, with prominent sesamoid fibrocartilage to be found in the deep surface of the tendon, and with articular cartilage acting as periosteal fibrocartilage. By contrast, at the site of the patellar tendon insertion (an extra-articular enthesis organ), periosteal fibrocartilage of variable prominence is present, depending on the shape of the bone near the enthesis, and the whole organ is closely related to synovium and fat pad.[7]



● **Figure 1.3** An enthesis, using the example of the Achilles tendon.

A classic example of the enthesis organ is the Achilles tendon, containing both types of fibrocartilage. While the posterior aspect of the calcaneus is coated by periosteal fibrocartilage, the "sesamoid" fibrocartilage is found opposite the posterior aspect of the calcaneus. The retrocalcaneal bursa has a triangular shape pointing caudally; it is delimited ventrally and dorsally by the periosteal and sesamoid fibrocartilage, respectively, and only on the roof by a bursal membrane.[3]

THE BLOOD SUPPLY AND INNERVATION OF ENTHESES AND ENTHESIS ORGANS

Just like cartilage elsewhere in the body, the fibrocartilage of enthesis organs can be generally regarded as avascular.[15] The aforementioned feature is very important because it in effect creates a "demilitarized immune buffer zone" at the sites of the highest stress, where the immunocompetent cells (activated easily by mechanical stress) are usually scarce.[16] Nevertheless, vessels still often penetrate fibrocartilage as a consequence of tissue damage, including age-related changes or inflammation.[17]

The invading blood vessels either come from the surface of the immediately contiguous tendon/ligament tissue (as well as from loose connective tissue or fat) or penetrate fibrocartilage from the bone marrow. In the latter case, vascularization is facilitated by a local (microscopic) absence of bone at the enthesis. This is a general feature of many attachment sites in elderly individuals.[17]

There is very little compact bone at fibrocartilaginous attachment sites. Consequently, the pattern of cancellous bone architecture is critical for the integrity of the tendon or ligament attachment.[9] There are no Sharpey's fibers – a matrix of connective tissue consisting of bundles of strong predominantly type I collagen fibers connecting soft tissue to the bone – at many entheses.[18] With the virtual absence of cortical bone at fibrocartilaginous attachments, there is simply insufficient hard tissue for Sharpey's fibers to get a decent connection to the bone. Instead of that, the firm attachment of tendon (or ligament) to bone (which is obviously the primary function of the enthesis) is made possible by a complex interdigitation of calcified enthesis fibrocartilage and bone at the attachment site and by the architectural pattern of the underlying bone spicules.[19] The number and arrangement of the spicules directly reflect the mechanical forces acting on the enthesis and is thus a key element of the anchorage mechanism. MRI evidence suggests that at sites of heavy load (*e.g.*, the Achilles and quadriceps tendons), the spicules are orientated along the direction of pull of the tendon.[20] Thus, the network of bone spicules in the proximity of an enthesis is functionally closely related to the adjacent soft tissues (similarly as the roots of a tree) and deeply involved in the mechanical function of an enthesis, confirming the theory of the enthesis organ once again.[9] The intimate vicinity of bone marrow to tendons or ligaments at entheses and the direct contact between them also allows stem cells in the bone marrow to access directly the soft tissue side of an enthesis,[17] providing an opportunity for tissue repair, which is triggered by the microdamage, a very common phenomenon at the tendon-to-bone insertion sites, sometimes leading to over-repair and new bone formation.

Although cartilage elsewhere, including articular cartilage that lines the ends of long bones, is known to lack a nerve supply, and fibrocartilage indeed is not really innervated, enthesitis might be very painful. This is due to the fact that nerve endings are located in the nearest proximity to the insertion site. Nerve endings may be located on the surface of the attachment site within the loose connective layer that is known as the epitenon. Peripheral afferent C-fibers and A-delta fibers have been identified in this area.[21] Another portion of the enthesis organ, which is documented to be innervated, is fat bodies lying deep to the attachment site at the insertional angle. As this fat is compressed through joint movement, the mechanical load through the decrease in the insertional angle stimulates the nerve fibers between the fat cells. Overstimulation of the proprioception nerve endings such as Golgi tendon organs, found within the ligaments and tendons, may also contribute to pain sensation. Pain may also originate from the bone underneath insertions, especially when there is bone damage or pressure changes within the bone due to disease states. Therefore, there are multiple possible sources of pain known in the enthesis organ, so pain may originate in several locations near insertions but not from the enthesis itself.

ENTHESES AND THE IMMUNE SYSTEM

Given the fibrocartilaginous and ligamentous/fibrous nature of entheses – and, therefore, no blood supply in the exact point of junction – the actual insertion region had not been thought to contain immunocompetent cells. Nevertheless, macrophages are known to be present in entheses. As mentioned previously, an especially important component of the enthesis organ