Engineering the Enthesis: Mechanical Constraints, Functional Objectives, and Biomaterial Design Strategies

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Abstract

Fibrocartilaginous entheses are heterogeneous connective tissues that link soft tissues to bone in key joints and are crucial for mobility where the available attachment area is minimal. Current replacements fail to sufficiently replicate the compositional and structural gradients of the native enthesis, which transitions from ligamentous tissue to fibrocartilage to mineralized tissue within millimeters. Tissue engineering and tissue characterization efforts have largely focused on replicating enthesis heterogeneity, often without explicitly considering how this heterogeneity supports specific mechanical and biological functions. In this Review, we first define the enthesis as a tissue that performs five key functions under the overarching role of dispersing stress at locations of pronounced stiffness change within joints. Using this functional perspective, we critically examine characterization studies across anatomically distinct fibrocartilaginous entheses, relating measured parameters to particular functions, emphasizing shared features across entheses, and highlighting location-specific differences where relevant. This analysis identifies the current state-of-the-art in enthesis characterization and exposes key gaps in how structure–function relationships are assessed. We then evaluate enthesis tissue replication strategies in terms of their ability to reproduce tissue heterogeneity and fulfill specific enthesis functions and argue that an important gap has emerged: the optimal design of enthesis replacements has rarely been guided by explicit performance objectives grounded in function. Finally, we propose an investigative protocol to address this gap, using the meniscal enthesis as a candidate model system. We anticipate that this framework will streamline design choices, advance enthesis tissue engineering, and motivate similar function-driven approaches for other musculoskeletal tissues.

Introduction

Entheses are specialized interfaces that connect soft connective tissues (such as ligaments, tendons, and menisci) to bone and enable force transmission across the musculoskeletal system. Restoring entheses remains one of the most challenging problems in orthopaedic medicine. These relatively small, seemingly simple junctions display remarkable engineering complexity. Within the space of only a few hundred microns, entheses integrate substantial spatial variations in structure, extracellular matrix composition, biochemical cues, cellular phenotype, and mechanical properties to enable the durable attachment between compliant soft connective tissues and mineralized bone. Beyond serving as anatomical transitions, entheses operate under extreme mechanical demands. They must repeatedly transmit physiological loads from

collagen-rich soft tissues to orders-of-magnitude stiffer bone without accumulating damage that could lead to catastrophic failure. Absent an appropriate functional mediating structure, the union of materials with such drastically different mechanical stiffnesses under these loading conditions would produce very high interfacial stresses and strain concentrations making the junctions subject to failure. Yet, the native enthesis is quite durable, reliably protecting the attachment site. This durability indicates that the defining function of the enthesis is not simply attachment; it is stress management across extreme stiffness mismatches. As a result, entheses enable load transfer, mitigating the expected damaging stresses and strains that would localize at sharp material boundaries, and are therefore critical to stability and mobility of the musculoskeletal system [1].

When soft connective tissues are damaged, clinical repairs typically focus on restoring gross continuity between the bulk soft tissue to bone using sutures, anchors, or screws depending on the anatomical location. While these procedures effectively reestablish mechanical connectivity, they do not restore the stress management capabilities of the native enthesis. Instead, a disorganized scar tissue forms that lacks the hierarchical structure, compositional spatial variations, and mechanical function of native soft to hard tissue interfaces [2–5]. As a result, soft connective tissue repairs are prone to fatigue failure or degeneration at the interface. This susceptibility is exemplified clinically by failures of anterior cruciate ligament reconstruction [6–8], high retear rate following rotator cuff tendon repair [9–11], and post-operative meniscal extrusions and failure [12,13].

To overcome this clinical challenge, substantial effort over the past several decades has been devoted to biomaterial-based strategies for enthesis repair and regeneration. While historically tissue engineering efforts in this area focused heavily on the bulk soft tissue [14,15], more recent efforts have explicitly targeted restoring the enthesis itself. Despite this shift in approach, clinically robust regeneration of functional entheses remains elusive, underscoring the need for a mechanistically informed framework for enthesis biomaterial design that prioritizes the stress management function of the enthesis for the improved attachment goal.

In this review, we synthesize our current understanding of native enthesis structure, mechanics, and response to loading through the lens of its stress management function. We first establish the anatomical and structural context of the enthesis relevant to this work, including the class of entheses considered and their defining architectural features. We then define the functional objectives that any enthesis must satisfy independent of anatomical location informed by mechanical constraints and experimental and computational observations across length scales. Building on these objectives, we summarize multiscale structural and compositional features reported for native entheses and identify where existing evidence suggests potential structure–function linkages. Using this framework, we critically evaluate existing biomaterial-based approaches for enthesis repair and regeneration with key illustrative examples. Finally, we conclude by outlining a function-driven path forward for the rational design of enthesis biomaterials.

Classification and Baseline Architecture of the Native Enthesis

In general, entheses are broadly classified into two major categories: fibrous entheses and fibrocartilaginous entheses [16]. Fibrous entheses are characterized by insertion of the soft connective tissue into a relatively large area of either the periosteum or the bone through mineralized collagen fibers without the presence of fibrocartilage [16,17]. The large area of insertion of these entheses is thought to be the principal mechanism of stress concentration reduction [16,17]. While they are associated with some of the largest muscles in

the body, these entheses are less commonly associated with soft connective tissue injury and repair requiring biomaterial support [16]. As such, this type of enthesis is not the focus of this work.

Fibrocartilaginous entheses, as suggested by their name, contain sites of fibrocartilage between the dense fibrous soft connective tissue and the bone. They are found in many of the crucial joints in the human body, including the ankles, the shoulders and the knees. These entheses form where connective space is limited, tend to endure continuous applications of relatively high stress, and, critically, do not naturally reform following current clinical procedures. It is for these reasons this type of enthesis is the exclusive focus of this review.

Fibrocartilaginous entheses [16,17] display substantial variation in cellular phenotype, extracellular matrix composition, architectural organization, and mechanical cues as one moves from through the tissue's four distinct but continuous zones:

Soft connective tissue (ligamentous) region (LIG),

Uncalcified fibrocartilage (UFC),

Calcified fibrocartilage (CFC), and

Subchondral bony region (SB).

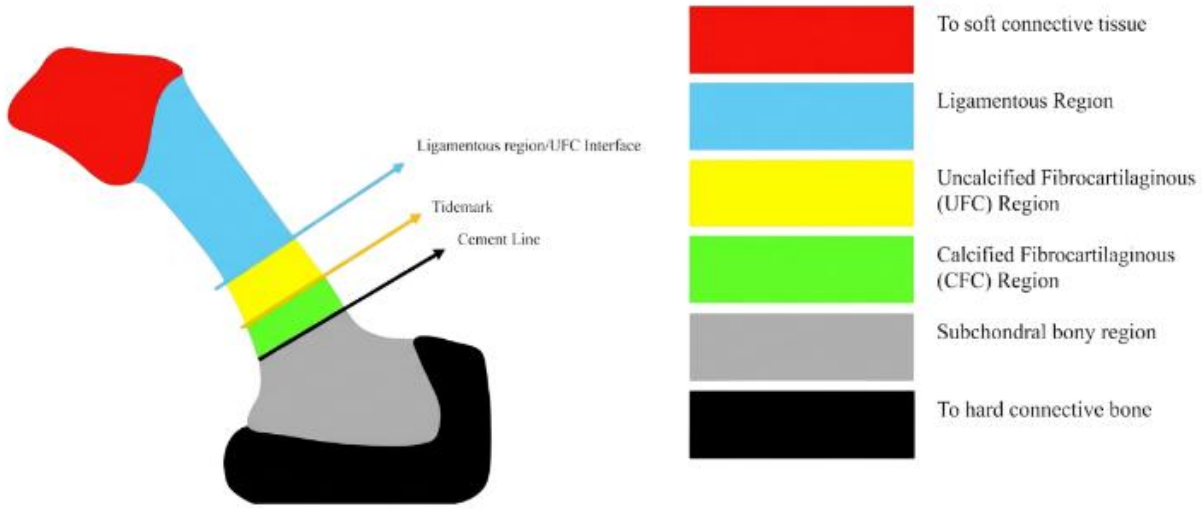

Figure 1:Schematic of a general enthesis structure, with subregions and inter-regional interfaces distinguished

Functional Objectives of the Native Fibrocartilaginous Enthesis

Across the musculoskeletal system, from the rotator cuff tendon insertions to the meniscal tibial attachments and beyond, native entheses operate under a common set of mechanical constraints dictated by their role connecting compliant soft tissues to rigid bone. Under the mechanical demands of musculoskeletal motion, entheses must transmit forces, accommodate mismatched deformations arising from extreme stiffness differences, maintain structural integrity under repetitive multiaxial motion, and withstand occasional supraphysiological loading events. While the enthesis is often described as functioning to reduce stress concentrations, this shorthand does not fully capture its functional role. Rather than serving simply as a passive stress concentration reducing feature, the enthesis fulfils multiple, interrelated functional objectives that arise due to the listed mechanical constraints. Synthesizing experimental and computational studies across length scales, we can surmise a set of interrelated functional objectives required of entheses, regardless of anatomical location. The following subsections define these functional objectives and summarize evidence supporting them.

Functional Objective 1: Limit stress/strain localization via stress dispersion

Experimental and computational evidence indicates that a primary function of the native entheses is to limit stress and strain localization at the soft–hard tissue interface in order to maintain attachment integrity under physiological loading. In regular tensile tests [18,19], meniscal entheses demonstrated distribution of tensile deformation across the subregions, and specifics in strain and failure between the entheses differed based on anatomical location, and thus loading profile, as opposed to a singular common point of failure. In pull-to-failure tensile tests across multiple fibrocartilaginous entheses, failure most commonly originates as bony avulsion rather than at the interface itself [20–22]. Under high-amplitude cyclic loading, the location of failure shifts toward the adjacent soft connective tissue, while the tidemark remains an infrequent failure site. These observations are consistent across anatomical locations. In supraspinatus tendon, meniscal, and patellar tendon entheses, experimental studies similarly show that failure under tensile or cyclic loading does not localize at the tidemark, even though this region represents a narrow zone of steep stiffness change. Furthermore, the enthesis experiences substantial shear stresses even under nominal tensile loading [23], which indicates a structure capable of resisting complex loading profiles without creating a failure origin point. At the microscale, nanoindentation studies demonstrate rapid increases in elastic modulus across the fibrocartilage zones over length scales of hundreds of microns [24,25], yet this mechanical contrast does not correspond to consistent failure initiation at the mineralization boundary [19,24]. Furthermore, within the CFC and SB region, alternating bands of higher and lower mineralization content and microscale stiffness exist, showing spatial variation of mechanical properties [26,27]. In contrast, when entheses suffer from osteoarthritis and lose local heterogeneity in microscale moduli and structure, their attachment integrity also suffers [28,29]. Together, these findings indicate that stress and strain are not preferentially concentrated at the interface itself under physiological loading conditions.

Computational studies provide additional support for this functional requirement by demonstrating that stress concentration at the enthesis is governed primarily by relative architectural parameters rather than absolute loading conditions. In a model of the rotator cuff tendon enthesis, Liu et al. [30] showed that a biomimetic stiffness gradient distributed both tensile and shear stresses more effectively simultaneously across the insertion than either a sharp stiffness contrast or a simple linear gradient. In a separate study [31],

stress concentration ratios were found to be sensitive to the relative length of the enthesis with respect to the adjoining soft connective tissue and to the proportions of its constituent sub-regions, but largely insensitive to absolute joint load, absolute enthesis length, or collagen fiber stiffness within physiological ranges. Taken together, experimental failure patterns and computational stress distributions support the interpretation that limiting stress and strain localization is a defining functional requirement of native entheses.

Functional Objective 2: Sustain function over prolonged cyclic loading

The entheses are constantly engaged in cycles of loading and unloading, and they have shown themselves to be very proficient at working in such a mechanical loading environment. Tensile cyclical tests on Meniscal entheses [32] featured stable cyclic creep and displacement responses under continuous cycles, and differences between the separate anatomical entheses do not compromise attachment integrity of the entheses. This relative indifference to continuous cyclical loading is further seen from enthesis in shoulders, which can function without failure even after 100,000 cycles when subjected to cyclical loads with amplitudes lower than 20% of maximum loading capacity [21]. At higher cyclic loadings, the entheses show gradual accumulation of damage instead of immediate catastrophic failure, originating in the softer regions like UFC and LIG region. The entheses have also shown to offset long term damages to collagen fibers in the softer subregions with replacement fibers in the same soft sub-regions [33], and mechanical stimulation have been shown to influence local macrophage induced healing for the entire enthesis [34]. In computational study [31], it has been noted that fatigue induced stress in the entheses do not scale directly with increasing number of cycles or load magnitude, but rather on the relative proportions of sub-regions and the way the enthesis is engaged in the joint it is part of. In tandem, these aspects of the entheses seem to ensure a nearly infinite work life in perfect working capacity.

Functional Objective 3: Regulation of failure mode and location under overload

The entheses are intrinsically designed to mitigate damage in the worst-case scenarios. This can be seen prominently in the fact that failure behavior of the entheses changes with loading rate [35], with both strength and toughness increasing substantially when the entheses experiences higher rate of strain accumulation [21]. Simulation study [31] predicts that the location of peak stress concentrations in the entheses changes under different loading conditions. This prediction has been corroborated in experiments: when subjected to catastrophic loading scenario, supraspinatus tendon enthesis has shown to fail in the bony avulsions predominantly. Even in the case of fatigue buildup from high amplitude cyclical loads, the failure occurs in the adjacent soft tissues, keeping the enthesis as intact as possible [21]. This phenomenon has also been noted in meniscal entheses [19,24]. The response to overload seems to be a resultant of multiple parameters in the entheses: studies show that removing mineralization reduced elastic modulus and ultimate failure load, while removing proteoglycans reduced stiffness and strength of the entheses, but not their toughness [21,36,37]. This is an effective evolution in the function of enthesis that allows it to function for the longest amount of time, even under disastrous situations.

Functional Objective 4: Remain mechanically engaged across multiaxial joint loading

The macroscale properties of the entheses change depending on the joint [38,39] it is situated in. In knee joint, with relatively simple joint movement profile, the meniscal entheses engages all its fibers equally

without bias [38,39], resulting in consistent endurance of tensile load by the meniscal entheses, which have been measured to be a consistent fraction of the applied load on the knee joint, with the fraction changing based on the joint angle [40]. The same meniscal entheses show changes in intra-ECM fluid pressure changing strongly with joint angles [35,38], further affirming total enthesis engagement under all loading. and However, in joints like in the shoulder [41,42] and the ankle [43,44]**, where the joints move in multiple directions, the entheses tend to engage their fibers in tiers, where some fibers engage before others. Rotator cuff entheses and Achilles tendon entheses also tend to have different tensile strains for different joint abduction angles** [42,43]**. Simulation study further shows that in the supraspinatus tendon enthesis** [45]**, the displacement required to engage all of the enthesis fibers changes significantly based on the angle of abduction of the shoulder joint. This indicates an effective evolution of enthesis structure-function relationship that goes beyond just microscale changes, but an awareness of the loading profile in a joint, and optimization at the largest scales to match the different loading profiles in different joints in the body.**

Functional Objective 5: Adapt to altered mechanical stimulation to preserve attachment function

The enthesis, during development [46] and in maturation, remains extremely sensitive to the loading environment it is subjected to, and quickly changes its characteristics to adapt to different mechanical stimulations. Computational modelling predicts that changing loading stimulations will result in redistribution of stress and deformation [31]. Under low loading conditions, the following changes take place: Proteoglycan content and collagen type II expression decreases in the fibrocartilage zone [41,47]. This is accompanied by increasing disorganization of collagen fibers in the LIG region and UFC [41,47–50]. In the bone zone, the number and the proliferation rate of chondrocytes decreases due to hypo-stimulation [47,51]. All cell types tends to lose their usual spherical morphology and becomes more oval in nature [41,47]. These changes occur in terms of days [52]. The microscale change is followed by macroscale changes over a longer period (months), with gradual demineralization in Calcified FC and SB [21,53], increased trabecular spacing, decreased overall area of UFC and CFC [49,51,54]**.** When entheses are exposed to above-average loadings, the opposite tends to happen [21,53,55]**. What we see from the changes is that the entheses changes strength and toughness, but retains overall geometry of attachment** [53]**, presenting an adaptive response to changing conditions instead of catastrophic responses. This response has its foundations from the cellular scale mechanosensitive response using primary cilia and hedgehog signalling** [56]**, that then accumulates to create larger scale effects over a longer period, allowing for flexible adaptation, which is nevertheless robust towards short term irregular stimulation events. This phenomenon suggests that the enthesis actively assesses the mechanical environment it is subjected to, and it responds to changes in a way that will optimize its function as a musculoskeletal attachment.**

In this review, we define the stress management function of the enthesis as the integrated satisfaction of these functional objectives across the full spectrum of in vivo loading conditions. This definition establishes the mechanical performance criteria that subsequent sections use to interpret native enthesis structure and to evaluate biomaterial-based strategies for enthesis repair and regeneration. We note that these functional objectives describe the mechanical requirements for durable load transfer at soft–hard tissue interfaces and do not encompass the full range of biological, developmental, and homeostatic functions performed by entheses.

Multiscale Structural and Compositional Organization of Entheses

Throughout the body across many different anatomical locations, native fibrocartilaginous entheses display a consistent multiscale structural and organizational logic that contributes to satisfying the functional objectives defined in Section 3. This logic as described in the enthesis literature broadly is characterized by the presence of recurring multiscale features. Although the precise mechanistic relationships between these features and the functional objectives are still under active investigation, their recurrence suggests a conserved biological blueprint enthesis stress management. This section first describes the shared structural and organizational features across entheses reported in the literature regardless of anatomical location. We begin describing architecture, including the presence of distinct regions, extracellular matrix compositional gradients, hierarchical structural organization, and specialized cellular phenotypes. We end the section by addressing how systematic variation of relative dimensions and compositional allow mechanobiological tuning of the enthesis to meet the requirements of joint-specific loading.

Transitions within the Enthesis

The subregions of the entheses do not transition discretely but are connected by cellular and compositional variations [57], indicating functional continuity. The UFC and CFC are separated by interdigitations known as tidemark [58], which matures from an intermittent band of mineral deposition into a highly localized zone of mineralization [33] [59]. The CFC/SB and LIG/UFC regions also have their own interfaces, though they have not been investigated to the same extent as the tidemark, with no known investigations done for LIG/UFC interface to the authors' knowledge. Interdigitations at these transitions increase enthesis toughness with some increase in stress conditions. [60–63].

Gradients present in enthesis

Entheses span stiffness values from tens to hundreds of MPa in soft tissue regions to around 20 GPa in bone [60,64]. This gradient in microscale stiffness occurs in tandem with the changes in mineralization content that initiates at the tidemark. In the CFC, calcium deposits increase from the tidemark towards the bone [60,65–67]. Calcification in enthesis occurs intermittently, forming a band of tissues at tidemark for young adults [33,59] and is regulated by connexin 43 [68] , Fgf 9 [69], sclerostin [70], and scleraxis [71]. Both CFC and SB shows alternating bands of high and low mineral contents in their respective regions, with more pronounced calcium content difference in CFC [26]**.** The relationship between mineral content and stiffness is not uniform across the enthesis. While local stiffness in calcified fibrocartilage and bone correlates with mineral content, the strength of this correlation varies between subregions.

Cellular phenotype gradients are prominent in the enthesis. The LIG region consists of fibroblasts intertwined with uniformly oriented collagen type I fascicles [33,72–74], that are phenotypically distinct from the fibroblasts in tendons and ligaments [75,76]. The fibrocartilaginous zones contain fibrochondrocytes and hypertrophic chondrocytes [1,77,78], which increasingly interact with mineral deposits in the CFC region. The subchondral bone region is composed of osteoblasts, osteoclasts and osteocytes embedded in collagen type I rich matrix [1,77,78]. In this region, hydroxyapatite content directs osteogenic differentiation and bone tissue formation [79]. This cellular phenotype gradient interacts with spatially distributed transcription factors and regulatory proteins to create and maintain the hierarchical

structure of the enthesis underlying its functions. The mineral density in the CFC dictates macroscale tensile deformation [27].

Collagen type distribution follows a complementary compositional logic. Type I collagen dominates the ligamentous region, providing high tensile load resistance through parallel, highly organized fiber bundles [1,77,78]. Although collagen type I is also present in the adjacent soft tissues, the work of Puetzer et al [75,76] demonstrated that cells from the LIG region have different phenotypes than those from the soft connective tissue resulting in different hierarchical collagen structure. Type II collagen characterizes both uncalcified and calcified fibrocartilage zones [78,80,81], where it associates with hyalectan and small leucine-rich proteoglycans [82] to provide compressive load resistance and flexibility. Type X collagen [1,77,78] is present in the pericellular matrix of hypertrophic chondrocytes in the calcified fibrocartilage , where it acts as a precursor to mineralization and guides osteogenic differentiation in the bone zone. The SB region itself has mainly type I collagen distributed within it, but the mineralization via deposition of calcium, increased cross-linkages, as well as the effectively isotropic distribution of the fibers make the SB region behave distinctly from the ligamentous region, acting as a stiff anchorage for entheses.

Proteoglycan enrichment represents another compositional gradient, concentrated in the fibrocartilaginous zones but absent in the ligamentous region [82]. Both uncalcified and calcified fibrocartilage contain hyalectan and small leucine-rich proteoglycans, with the uncalcified fibrocartilage additionally containing glycosaminoglycans [83]. The concentration of chondroitin sulfates increases progressively toward the calcified fibrocartilage zone. Proteoglycans facilitate collagen fiber cross-linkage, enhance water retention for shock absorption, and regulate mineralization progression. The proteoglycan gradient also informs the water content gradient to some extent, though this has not been directly investigated. These gradients in turn influence the stress dispersion functions of the entheses.

Evolution of fibrous architecture

Fibers in the entheses are made of various collagens. They create a multi-scale structure with interactions that influence the structure and function of the entheses. At the nanoscale, collagen fibrils [75,76,84] (triple helix structures approximately 1–2 nm in diameter) interact electrostatically with mineral crystals (hydroxyapatite) and proteoglycans, forming mineralized composite structures whose elastic moduli exceed those of collagen or mineral alone [85,86].

At the microscale, collagen fibrils assemble into fibers and fiber bundles whose organization and orientation control regional stiffness, toughness, and load transfer. The fibers of the LIG region are continuous with the soft connective tissue, with similar fiber counts on both side of the boundary [87]. In this region, collagen fibers are highly organized into parallel bundles with relatively uniform orientation [33,72–74], enabling resistance to uniaxial tensile loading. Collagen type I fibers in the LIG region also slide over each other and rotates at lower strain, to absorb tensile energy before the fibrocartilage zones need to engage, which contributes to stress dispersion [72].

Moving to the fibrocartilage regions, collagen fibers begin to disperse with increasing angular deviation [60,65,72,88], resulting in a more isotropic structure that assists the resistance of compressive loads and facilitates mineralization and cross-linkage of mineralization as fibers enter the CFC [74,89,90]. The orientation of the collagen fibers at the tidemark is correlated with elastic modulus: the more perpendicular the fibers in the uncalcified fibrocartilage are to the tidemark, the less steeply the elastic moduli change across the tidemark [25]. This organization also leads to increased tensile strength and ultimate load bearing capacity [18,19,32,64]. In contrast, entheses with UFC collagen fibers less perpendicular to the tidemark tend to distribute stiffness between elastic and shear resistance more evenly [45], but show steeper

microscale tensile elastic moduli change along the tidemark. The graded disorganization of fibers in fibrocartilage zones increase the toughness independently from mineralization [36]. Increased disorganization at uncalcified also provides greater stress dispersion at lower elastic strength and vice-versa [45,91]. The UFC fibers continue to the calcified fibrocartilage zone unchanged in structure and composition [33].

At the macroscale, the fibers of the entheses show adaptive features to accommodate varying loading conditions. Supplemental fibers around supraspinatus tendon enthesis distribute mechanical stress and increase ultimate load and tensile strength [60,91,92]. The anatomical location also influences the way the fibers of the entheses engage. In meniscal entheses, all of the fibers engage, regardless of how the knee is bent [38,39]. However, in the shoulder and ankle joints, the fibers of the entheses engage more selectively [42,43,45], and the stiffness and elastic moduli of the entheses in these joints also tend to change depending on the joint angle [21,42,45], a consequence of the selective engagement of fibers. The fibrous architecture in the enthesis thus acts at multiple length scales.

Hierarchical organization in enthesis dictates its functions

The cellular, compositional and fiber architecture gradients in the entheses collectively generate the multiscale hierarchical structure that contributes to enthesis function. At the nanoscale, compositional gradients regulate fibrillar organization and cross-linking through proteins that are more active in entheses than in the soft connective tissues [74]. Experimental disruption of these pathways reduces macroscale strength and stiffness without significantly affecting toughness [21], whereas combined demineralization and proteoglycan removal leads to losses in toughness in addition to strength and stiffness. These findings demonstrate that mineralization and matrix composition act in a complementary manner, with distinct hierarchical contributions to different mechanical properties.

At the mesoscale, the transition between the subregions contributes to the function of the enthesis. The interdigitation of the transition between the zones have been shown to increase toughness [60–63]**.** These interdigitations occur at the peak vs wavelength ratio of 0.2 that optimizes maximum gain of toughness for the smallest increase in stress concentration. Additional mesoscale mechanisms, such as sliding and rotation of collagen type I fibers in the ligamentous region at low strain, absorb tensile energy prior to engagement of the fibrocartilaginous zones, further dispersing stress across the interface of the enthesis [72].

At the macroscale, hierarchical organization ensures that the overall stress concentration ratio in the enthesis is not sensitive to absolute load on the joint, the absolute length of enthesis and the stiffness of collagen fiber, as long as those values are within the physiological limits [31]. Loss of higher-order structural features, such as supplemental fiber populations, leads to reduced insertion area, decreased stiffness, and diminished ultimate tensile load [60,91,92]. Mechanical stimulation studies further indicate that while cellular-scale properties adapt rapidly to altered loading, changes in macroscale mechanical behavior occur over longer timescales [52], which suggests the hierarchical structure of the entheses provides a buffer to offset the detrimental effects of its ability to adapt to changing loading conditions. While all these studies establish that hierarchical organization is essential for enthesis function, they do not identify which specific features exert first-order control over function under different loading conditions.

Organizational Feature	Conserved Logic Across Entheses	Systematic Variability Observed	Representative Entheses Observed	Functional / Mechanistic Implication	Citations
Zonal architecture	Continuous transition from	Absolute zone thickness and	Supraspinatus tendon enthesis	Associated with gradual load	[1,27,58,72,77,93–103]

Table 1:Structural properties of the entheses with respect to function

	ligamentous tissue → uncalcified fibrocartilage → calcified fibrocartilage → bone	proportions vary with joint function	(shoulder); Achilles tendon enthesis (ankle); meniscal tibial enthesis (knee)	transfer and reduced stress concentrations	
Mineral gradient	Mineralization initiates at the tidemark and increases toward bone	Degree and spatial pattern of mineral heterogeneity vary between entheses	Supraspinatus tendon enthesis (shoulder); Achilles tendon enthesis (ankle); meniscal tibial enthesis (knee)	Correlated with stiffness transitions and interfacial load sharing	[65,67,70,104]
Stiffness gradient	Orders-of-magnitude increase in stiffness from soft tissue to bone	Slope of stiffness transition differs across anatomical sites	Supraspinatus tendon enthesis (shoulder); Achilles tendon enthesis (ankle); meniscal tibial enthesis (knee)	Associated with mitigation of stress amplification at the interface	[25,30,63, 81,84]
Cellular phenotype gradation	Fibroblasts → fibrochondrocytes → hypertrophic chondrocytes → osteogenic cells	Extent of phenotype overlap not systematically quantified	Supraspinatus tendon enthesis (shoulder); Patellar tendon enthesis (knee); meniscal tibial enthesis (knee)	Associated with spatial regulation of matrix deposition and mineralization	[33,46,57,73,74,78,81,105]
Collagen type distribution	Type I dominant in ligamentous and bone regions; Type II/X enriched in fibrocartilage	Relative abundance varies with joint function	Supraspinatus tendon enthesis (shoulder); Achilles tendon enthesis (ankle); meniscal tibial enthesis (knee)	Associated with tensile vs compressive load resistance	[78,81]
Proteoglycan enrichment	Concentrated in fibrocartilaginous zones	Gradient magnitude varies across entheses	Supraspinatus tendon enthesis (shoulder); Achilles tendon enthesis (ankle); meniscal tibial enthesis (knee)	Associated with hydration, shock absorption, and mineral regulation	[64,78, 79,102]
Fiber orientation gradient	Progressive increase in angular dispersion approaching the tidemark	Degree of fiber recruitment depends on joint geometry and loading	Supraspinatus tendon enthesis (shoulder); Achilles tendon enthesis (ankle); meniscal tibial enthesis (knee)	Associated with toughness, stress dispersion, and failure resistance	[57,107,108]
Interdigitated interfaces	Wavy, interlocking interfaces between zones	Peak-to-wavelength ratios vary, especially across species	Supraspinatus tendon enthesis (shoulder); Achilles tendon enthesis (ankle); meniscal tibial enthesis (knee)	Associated with increased toughness at modest stress increases	[58,72]

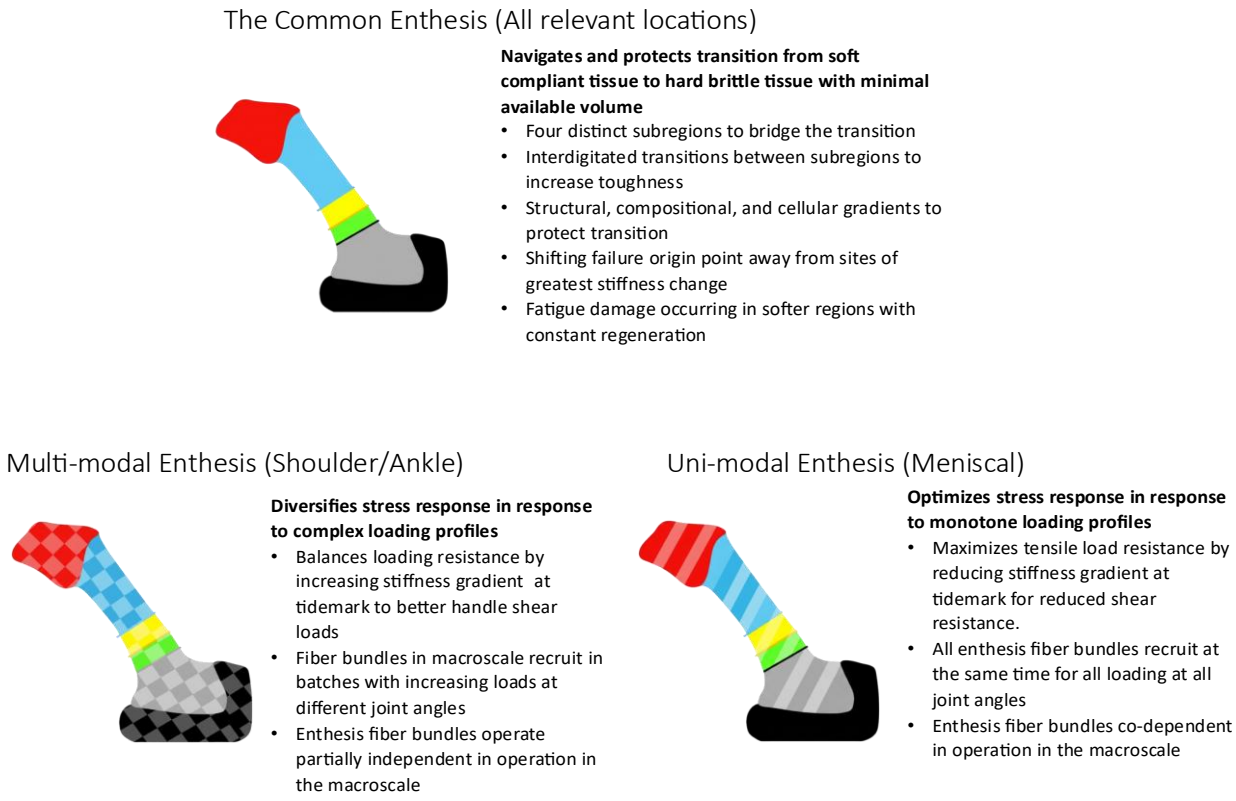

Figure 2: Overview of Enthesis function and notable characteristics

Under investigated aspects of enthesis structure characterization

Error! Reference source not found. presents a short summary of the multiscale features present in the enthesis and how they may contribute to the essential functions of the enthesis. The table does not comment on the relative significance of these features. The enthesis is a complex structure with multiple parameters and gradients that act both on their own and in conjunction with each other to dictate the stress dispersion function of the enthesis, which means all the structural and compositional parameters present in the enthesis likely contributes to the development of its function in some way.

However, to adequately understand the structure-function relationship of the enthesis, as well as to plan an effective replication for failed enthesis, the relative significance of the influences of these various features on function of the enthesis need to be investigated. To the author's knowledge, such an investigation has yet to take place in the context of enthesis structure and function. The replication efforts on the enthesis, discussed in the next section, have focused on the act of emulating one or more features of the enthesis, without deliberately mentioning a particular prioritization of which features need to be emulated primarily to replicate enthesis function.

Enthesis Repair and Replication Strategies Through a Functional Lens

The importance of maintaining native characteristics of the meniscal enthesis after repair or replacement procedures has motivated efforts for engineering strategies capable of restoring enthesis-like structure and function. Early investigations [109–115] of tendon and ligament replacement scaffolds established foundational biomaterial approaches to repair, but recent work by Puetzer et al [116] demonstrates that entheses have distinct structural, cellular, and mechanical features that are not fully captured by ligament and tendon repair structures. As such, there is a need for investigation of enthesis specific design strategies.

Many different approaches have been undertaken, ranging from biomaterial augmentation of clinical procedures, like suturing, to development of biomaterials as provisional extracellular matrix to guide entheses like tissue formation by endogenous cells. Enthesis complexity demands that the instructional ECM also has some degree of complexity. Across the literature, repair and replication approaches differ primarily in how much the biomaterial replacement has spatial and hierarchical organization deliberately controlled to emulate the native tissue. While functions such as stress dispersion, resistance to cyclic loading, failure regulation, and adaptability to changing loading environments are often discussed, they are rarely prescribed explicitly as design constraints. Instead, these functions tend to emerge implicitly as a consequence of structural or compositional choices. To synthesize this body of work without inferring design intent, strategies are organized below into categories defined by the degree and scale of deliberate control over enthesis-relevant phenomena.

Biomaterial Augmentation to Existing Clinical Procedures

The most prevalent clinical approach to enthesis repair remains suturing the torn soft tissue to the bone which restores the macroscopic attachment of the soft tissue to the bone. Such strategies rely on endogenous healing processes to regenerate interfacial tissue, despite the fact that the biological and mechanical environment during adult repair differs significantly from developmental enthesis formation. Several studies have explored modifications to standard suturing, demonstrating improved functional outcomes. Modification of suture materials, including the use of magnesium alloy threads, has been shown to improve inflammation response and promote more enthesis-like tissue repair, likely due to controlled Mg^{2+} ion degradation [117]. Nevertheless, such approaches remain focused simply on connection between the soft tissue and bone and do not introduce enthesis-like organization or function.

Injectable supplements delivered to the repair site have been widely investigated as an augmentation to suturing. These injectables have come from donor sources [118–120], platelet-based formulations [121,122], exosome mixtures [123–127], and injectable hydrogels [128–133]. These supplements may enhance regeneration and may support adaptation to changing loading conditions. However, the formation of scar tissues prevents further functions from being properly replicated.

Another group of augmentation involves biomaterials such as films or scaffolds applied over and around the repair site. These structures include demineralized bone and ECM scaffolds from donor sources [134–140] , adhesive films [141–143], polymer and composite grafts [144–154], collagen scaffolds, stem cell sheets [155–160], and bio-ceramic structures [161–166]. Such materials can aid in stress dispersion in the initial implantation period, but scar tissue formation still occurs. Additionally, these approaches do not attempt to recreate interfacial hierarchy or graded mechanics.

Biological Templates with Inherited Hierarchy

A second class of biomaterial strategies for enthesis replacements relies on the pre-existing structure and organization of excised tissue grafts, based on the assumption that their inherent hierarchy and structure may support regeneration. Minimally modified grafts include small intestine submucosa [167], interstitial fascia [168], amniotic membranes [169], tendon grafts [170] entheses extracted from other joints [171], as well as fully decellularized grafts from cancellous bone [172], enthesis from other joints [173], dermal ECM [174], and the Achilles-cancellous complex [175]. These scaffolds preserve collagen organization, porosity, and, in some cases, residual mineral distribution from the source tissue, which can contribute to improved integration relative to synthetic materials. Most of these grafts undergo additional post-processing, such as partial or full remineralization and protein incorporation [176]. These modifications are intended to introduce compositional heterogeneity, bias cell differentiation toward fibrocartilaginous or osteogenic phenotypes, and improve load transfer across the interface. While such grafts may provide some biological guidance, relying on endogenous cell infiltration, their functional outcomes are suboptimal. Despite improved structure relative to standard fixation, these constructs often are not as durable as the native tissue. To increase biological integration, these biomaterials may be seeded with cells just prior to implantation [177–181] or developed in-vitro to allow for controlled differentiation [182,183]. These approaches generally perform better than acellular implants, especially when modified to provide some compositional and structural gradient basis [183]. Other in vitro efforts include scaffold-less ligament constructed made of bone marrow derived mesenchymal stem cells anchored in culture solution [184] and a porcine dental dECM based bioink used to bioprint biphasic scaffolds [185]. Across this category, functional improvements arise implicitly from preserved or enhanced biological hierarchy, but mismatches in structural parameters limit full functional replication. These limitations underscore the importance of matching structural parameters, not just biological composition for proper enthesis function.

Homogeneous Biomaterial Enhancement Strategies

In contrast to biologically derived templates that inherit native hierarchy (Category II), the strategies described here rely on engineered biomaterials whose properties are enhanced uniformly across the construct, without spatial patterning or preservation of enthesis-specific organization. The underlying premise is that improving bulk mechanical strength, biological compatibility, or regenerative signaling can enhance repair outcomes, even in the absence of explicit interfacial patterning. While these strategies often yield improvements relative to untreated repairs, the lack of spatial control limits their ability to reproduce enthesis-like structure and function.

Metal-based enthesis repairs represent an example of this approach. Metals have been used as a permanent connection, prioritizing macroscale load connection and load transfer. Examples include titanium implants [186], which improved some osteointegration, and biodegradable magnesium screws [119]. These materials fulfill the overall connectivity requirement, much like sutures. Additionally, the use of metals may aid in management of failure under extreme loading.

Beyond metals, homogeneous enhancement strategies have been extensively explored using polymeric and hydrogel-based systems. Hydrogels based on alginate [187], decellularized tendon ECM [188], chitosan [189] have been used alone or with mineral or nanomaterial additives including hydroxyapatite and graphene oxide to promote mineralization and increase mechanical stability. Injectable thermosensitive hydrogels constitute a related subclass of materials. Materials based on oxidized hyaluronic acid [190], chitosan-gelatin-glycerol phosphate complex [191], methylcellulose-PVA-PVP complex [191], and PEG hydrogels [192] have been used for this application. The administration of bioactive materials and drugs have shown increase in osteogenic potential, partial matrix remodelling in ACL and tuneable

chondrogenesis and osteogenesis potential when applied in vivo. These additives have also been supplemented with heparin and other bioactive agents that resulted in increased cell compatibility and the provision of time-delayed drug release [189].

Homogeneous biomaterial enhancement has also been applied via electrospun scaffolds. Electrospun PCL and PLGA scaffolds doped uniformly with ZnO nanoparticles have shown enhanced improved bioactivity and anti-bacterial effects [193], while graphene oxide doped fibers have shown enhance cell response and matrix deposition [194]. In these studies, the primary focus has been on the influence of scaffold chemistry on regenerative pathways, and spatial control of doping or architecture was deliberately avoided. While the fibrous morphology itself can contribute to some degree of stress distribution under low loading conditions, this effect arises implicitly from the base scaffold structure rather than from deliberate interfacial design.

Engineered Gradient Based Biomaterial Strategies

A major thrust in enthesis repair and replication has been the introduction of engineered spatial gradients in biomaterial composition, most commonly mineral content or biochemical factors, to better approximate the transition from soft connective tissue to bone. Importantly, these approaches do not vary a single enthesis-relevant parameter in isolation. Instead, they impose compositionally driven gradients that inherently and implicitly couple multiple enthesis phenomena, including stiffness, strength, porosity, transport, and local biochemical environment.

Mineralization gradient intensive structures

Spatially controlling mineralization in the construct is the first and most prevalent biomaterial strategy. These efforts try to emulate stiffness and mineral control increase along the length of the entheses from soft tissues to bones. Early efforts relied on calcium phosphate cements and related derivatives, in which a mineral-rich region acted as a bony anchor while softer regions interfaced with tendon or ligament tissue [184,195,196]. Additional approaches introduced mineral gradients through partial submersion techniques [197], electron beam evaporation [198], tape-casting [199], crystalline application [76,200–202]. Of these, it was shown that tricalcium phosphate and brushite cements [184,196,201,202] tended to lack tissue level organization or durability, despite establishing mineralization gradient. Hydroxyapatite-based strategies sought to improve biocompatibility by incorporating a mineral phase more closely aligned with native bone. Gradients were generated using cyclic submersion [203], collagen matrix mineralization [204], wet bath doping during electrospinning [205], spatial control of droplet spraying [206], using fibers with varying HA contents [207,208]. Relative to calcium phosphate cements, these constructs demonstrated improved cellular response and integration.

More biomimetic approaches have attempted to induce mineralization *in situ* within organic scaffolds, thereby preserving aspects of native collagenous architecture while introducing spatially graded mineral content. Examples include the use of concentrated simulated body fluid on silk fibroin scaffolds [209,210] polyaspartic acid–mediated mineralization of collagen scaffolds with partial crosslinking [211], , and fibrin-based systems in which gradual transitions in mineral exposure outperformed abrupt interfaces [212]. These strategies improve interfacial continuity and can enhance stress dispersion relative to discretely mineralized constructs.

Biochemical and Compositional Biomaterial Strategies

A parallel class of gradient strategies replaces mineral variation with spatially patterned biochemical cues, including growth factors, ECM components, or functional chemical groups. These spatially controlled changes influence cell phenotype, thus creating a gradient of cellular heterogeneity in addition to the

compositional differences. Single-cartridge hybrid bioprinting approaches have demonstrated continuous gradients by layering distinct bioinks within a single deposition stream [213]. , while layered hydrogel systems with varying precursor ratios have been used to create compositional gradients after photopolymerization [214]. Refinement of this approach included incorporation of growth factors and media in the precursors [215] followed by partial crosslinking strategies that permit controlled diffusion between layers to generate smoother transitions [216–218].

Electrospun layered gradients represent a fibrous analogue to this approach. Gradients have been generated using distinct fiber blends, such as silk fibroin combined with PCL derivatives [219], and through chilled gelatin systems incorporating gradients of bioglass and methacrylated collagen prior to UV curing [220]. Bioreactor-based post-processing further extends this concept by inducing cellular gradients through differential culture conditions without pre-patterned material heterogeneity [221,222].

Structural Microarchitecture Control

Another important subset of the literature focuses explicitly on microarchitecture control via fiber orientation, mechanical stimulation [223], anisotropy, and pore-scale gradients, independent of composition. In hydrogels, fibrin-based systems have been freeze-dried with spatial NaCl distributions and templated rods to create orientation-specific bilayers [224], and gradual transitions between anisotropic and isotropic regions have been shown to improve mechanical strength relative to abrupt changes [212]. Collagen-GAG interactions have been mimicked using distinct fiber-based composites for heterogenous replication, leading to increased fracture toughness through crack-deflection mechanisms [225,226]. This remains the only work in the reviewed literature that explicitly targeted toughness as a primary functional objective**.**

In fiber-based systems, microarchitectural control has been achieved through layer-by-layer melt electrowriting with depth-dependent pore sizes [227], sinusoidal deposition patterns that tune elasticity and microscale toughness [228], capillary force lithography to generate microchannels supporting oriented tenogenesis [229], annealing to modulate strength and elongation via filament density [230], and magnet-assisted electrospinning that enables spatial control of fiber orientation for PCL, PEG, and cellulose fibers [231]. These approaches demonstrate that microarchitecture alone can influence mechanical behavior and cellular organization, though mimicking the UFC remains a challenge.

Multi-Phenomenon Integration Strategies

A subset of enthesis replication efforts have sought to integrate multiple gradients simultaneously within a single biomaterial construct. These strategies differ from gradient–based approaches described earlier in that they attempt to introduce structural variations in addition to other gradients, rather than relying on a single gradient to implicitly generate multiple effects. Several investigations have highlighted the consequences of omitting structural guidance even when compositional gradients are present, demonstrating deficiencies in replacement microstructure and mechanical function [232,233]. These observations have motivated approaches that combine spatial patterning with architectural or mechanical cues. For example, gelatin-based fiber systems collected using magnetic U-collectors have been mineralized using nano-hydroxyapatite solutions to produce region-specific differentiation responses [234], which created zone specific stem cell differentiation. Related biomaterial approaches have generated structural and biochemical gradients using core-shell electrohydrodynamic deposition of PCL fibers where pore size variation and regional distribution of growth factors induced structural and biochemical gradients [235]. More elaborate integration strategies have combined structural organization, mineralization, biochemical patterning, and mechanical stimulation. A series of studies by the Hailey group employed

collagen–GAG hydrogel platforms with anisotropic pore architectures generated via directional freezing, mineral gradients introduced through calcium phosphate infusion, biomolecular gradients immobilized using carbodiimide chemistry, and cyclic mechanical loading applied following MSC seeding [236–239]. Additional examples include hierarchical PCL/PLGA scaffolds incorporating GelMA and HAMA hydrogels, which introduced mineral and biochemical gradients but lacked fine microstructural fiber guidance and robust mechanical stimulation, resulting in less than optimal performance in vivo [240]. Meniscal enthesis–specific constructs have combined bone-plug-based mineral gradients, bifluid culture to impose biochemical variation, and axial tensile loading to induce partial fiber alignment [241–243]. Recent work [244,245] on enthesis included controlling chemical, physical and cellular gradients using a novel tri-fluid bioreactor, leading to increased agreement of replicant tissue structure to native enthesis, although the construct was lacking in elastic modulus and ultimate tensile load capability by orders of magnitude. Axial tensile loading showed oriented fiber formation at the outer rim of the construct and not in the middle, highlighting the need for microscale structural guidance. Across these studies, multi-phenomenon integration enables simultaneous engagement of stress redistribution, adaptation to changing loading conditions, and limited failure regulation. However, because multiple parameters are introduced concurrently, it remains unclear which features are necessary, sufficient, or redundant for achieving enthesis-like function.

Assessment of Functional Outcomes in Enthesis Repair Strategies

Across all categories, stress dispersion, failure management, and adaptability to changing loading environments tend to arise implicitly as a consequence of structural organization rather than from explicit functional prescription. Toughness under cyclic loading has been deliberately targeted in only one identified study [225]. More broadly, the biophysical and biochemical gradients of the ECM are recognized as key drivers of tissue formation [246–248], emphasizing both the promise and the challenge of enthesis biomaterial design. These observations motivate the need for analytical frameworks that identify which parameters dominate enthesis function.

Biomaterial Strategy	Primary Design Logic	Target Enthesis Features	Functional Objectives Addressed	Key Limitations / Gaps (Why Native Performance Not Reached)	Representative Literature
Biomaterial Augmentation to Existing Clinical Procedures	Restore macroscopic attachment and accelerate endogenous healing through adjunct materials	Connectivity at soft tissue–bone interface	Improved early fixation; limited adaptation through enhanced regeneration	No engineered interfacial hierarchy; scar tissue formation; absence of graded mechanics or microarchitecture	[117–166]
Biological Templates with Inherited Hierarchy	Leverage pre-existing biological organization from grafts or ECM	Native-like collagen architecture; porosity; residual mineral (in some cases)	Partial stress redistribution; improved biological integration	Structural parameters inherited from non-target tissues; mismatch with local loading; limited durability and failure regulation	[167–183]
Homogeneous Biomaterial Enhancement Strategies	Uniform enhancement of bulk material properties (mechanical, biological, or chemical)	Global stiffness, strength, bioactivity	Improved early stability; limited failure resistance under extreme loading	No spatial mediation; absence of gradients and hierarchy; functions arise only implicitly	[119,184,186], [188–194]
Engineered Gradient–Based Biomaterial Strategies	Introduce spatial gradients in composition that implicitly couple multiple properties	Mineral content; stiffness; biochemical signaling	Partial stress dispersion; improved integration across interface	Parameter coupling prevents attribution; stiffness, transport, and chemistry not independently controlled	[76,184,185], [195–211], [214–222,249],
Structural Microarchitecture Control	Explicit control of fiber orientation, anisotropy, and pore-scale architecture	Collagen alignment analogs; anisotropy; microstructural transitions	Stress redistribution; enhanced toughness (limited cases); guided cell organization	Composition and biochemical gradients often absent; limited control of multi-axial loading response	[223–231]
Multi-Phenomenon Integration Strategies	Concurrent incorporation of multiple gradients and/or structural cues	Structure, mineralization, biochemical signaling, mechanical stimulation	Simultaneous engagement of stress dispersion, adaptability, and partial failure regulation	Parameter sufficiency unclear; interactions between features unresolved; microscale fidelity incomplete	[212,234–245], [250,251]

Table 2: Biomaterial design strategies: Aims, successes and limitations

The Disconnect Between Enthesis Characterization and Replication

The prior sections have reviewed two major spheres of enthesis research: characterization of native enthesis structure and function and biomaterial-based strategies for enthesis repair and replication. While each body of work has advanced substantially, a critical disconnect remains between them. Specifically, existing replication efforts rarely incorporate prior knowledge or informed assumption of which structural or material parameters are most crucial for emulating enthesis functions. Instead, design choices are often

made to mimic certain structural or material features without explicit prioritization of parameters based on ***functional*** evidence. This lack of parameter prioritization represents a fundamental gap in the organization of enthesis research. Without a framework to identify which features exert dominant control over enthesis function, replication efforts risk becoming increasingly complex without corresponding gains in functional performance. As a result, progress is frequently measured by the addition of structural or compositional features rather than by demonstrated improvement in stress management or attachment performance.

As a biological heterogenous structure, the enthesis contains a multitude of different parameters that can be replicated. Attempting to emulate all of these features simultaneously is neither practical nor efficient, and such an approach obscures the identification of minimal design requirements. To enable meaningful comparison across studies and guide rational design, a standard is needed by which replication strategies can be evaluated relative to native enthesis function.

Bridging this gap requires addressing two fundamental questions:

1. Which structural and material features of the enthesis contribute most significantly to its functional roles?
2. What biophysical and biochemical cues need to be incorporated into the biomaterial structure to enable these features to emerge during maturation?

Answering these questions is essential for establishing design principles that move enthesis repair beyond accumulation of complexity and towards functionally informed prioritization in prospective replacements.

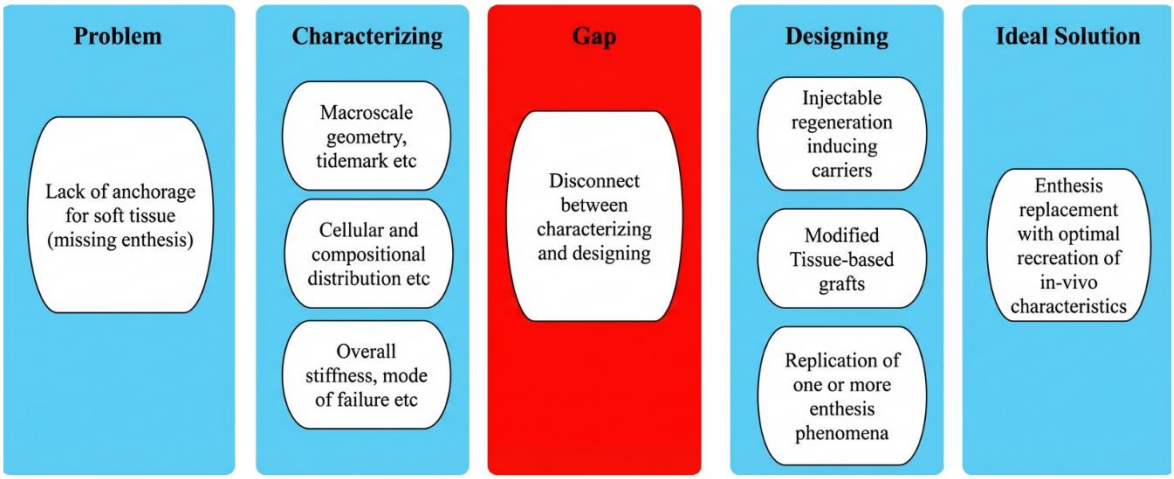

Table 3: Enthesis research gap: While extensive efforts have quantified multiscale structural and material parameters of the native enthesis, replication strategies rarely incorporate prior prioritization of these parameters based on functional dominance. As a result, functional outcomes tend to emerge implicitly rather than through function-driven design.

Toward Rational, Function-Driven Enthesis Biomaterial Design for Next-Generation Enthesis Engineering

A function-driven framework for enthesis biomaterial design requires that replication strategies be guided by parameter prioritization rather than by the accumulation of structural or compositional features. As a biologically heterogeneous structure, the enthesis contains a large number of potentially replicable parameters. Attempting to reproduce all observed features simultaneously is neither practical nor efficient and obscures the identification of minimal requirements necessary for functional performance. Progress towards the ideal enthesis replacement therefore requires a shift from imitation towards rational selection of parameters that exert dominant control over enthesis function.

Within this framework, functional performance serves as the primary criterion for evaluating parameter importance. Outputs such as stress dispersion at mechanically critical locations provide a basis for assessing whether specific structural or material features meaningfully contribute to enthesis function. Because many enthesis parameters are intrinsically coupled, experimental approaches that rely on independent variation of inputs are limited in their ability to establish dominance relationships. Computational modeling provides a necessary abstraction for isolating and ranking parameter influence under controlled loading conditions, enabling identification of reduced parameter sets capable of reproducing key functional behaviors. Experimental characterization should be guided by functional relevance. Structural, compositional, and mechanical properties should be measured in a way that determines their functional significance. Additionally, biomaterial design must consider which biophysical and biochemical cues are required to ***enable*** these prioritized features to emerge during tissue development, recognizing that mature enthesis function arises through mechanical and biological processes rather than static material properties alone.

This framework does not prescribe specific materials, fabrication techniques, or implementation pathways. Instead, it establishes a set of governing principles for rational enthesis replication: explicit linkage between characterization and function, prioritization of dominant parameters, and evaluation of replacement strategies against functional benchmarks rather than morphological similarity. By framing enthesis biomaterial design around function rather than feature accumulation, this approach provides a coherent way to integrate characterization and replication efforts. Further, it establishes the conceptual foundation necessary for developing tools capable of identifying which parameters are necessary and sufficient for achieving enthesis-like function, thereby enabling systematic progress toward rational, functionally informed replacement strategies. Adoption of such a framework reframes enthesis biomaterial development as a design problem focused on functional dominance and development rather than one focused on reproducing structural complexity alone.

Conclusion

In this review, the fibrocartilaginous entheses were reviewed for advances in characterization, modelling and replication efforts. By analysing the state-of-the-art on the investigations on understanding the enthesis, this review developed a holistic framework to defining enthesis function based on results from work that were not previously connected and interpreted in the approach taken by the authors. Using this view, current advances on enthesis replication and understanding were assessed, which led to the presentation of a critical gap in the overall research scenario, where results from characterization and modelling of the entheses were not optimally translated into replication design and framework, a gap that arises primarily from emphasizing on mimicking enthesis complexities, rather than a proactive approach to incorporating the essential

functions of the enthesis in the design. Finally, the review offers a protocol to prioritize enthesis parameters in terms of influence on key functions necessary in a replacement and use this information to provide function-driven Enthesis Biomaterial Design. This review thus compiles key findings from the enthesis tissue engineering advances till date in a view of functional performance, identifies critical gap in the research that requires immediate consideration, and offers an approach to fulfil said gap. The outcomes in this review will aid future research on enthesis engineering, and the approach undertaken can be applied to other musculoskeletal tissues where optimal design is yet to be achieved.

Author contributions

Muhtadi Munawar Zahin: Conceptualization, Investigation, Methodology, Data Curation, Visualization, Validation, Writing-original draft, Writing-review & editing

Benjamin B. Boesl: Supervision, Writing-review & editing

Darryl A. Dickerson: Conceptualization, Resources, Supervision, Writing-review & editing, Project administration, Funding acquisition

Conflicts of interest

The authors state that “There are no conflicts to declare”.

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