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Anisotropic Collagen Fiber Scaffolds as A Biomimetic Platform for Functional Tendon and Ligament Regeneration

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Abstract

Collagen is the backbone of tendon and ligament tissue. It makes up most of the extracellular matrix and gives these structures their strength and organization. So, it makes sense to build scaffolds from collagen when trying to repair torn tendons or ligaments. But there is a catch: pure collagen on its own is rarely strong enough to handle the forces the human body throws at it, and most scaffolds lack the aligned fiber structure that native tendons depend on. In this study, we look at how researchers are designing anisotropic collagen fiber scaffolds to overcome these problems. We start by describing what tendons and ligaments actually need to survive in the body—not just tensile strength, but resistance to fatigue fracture, creep, and the surprisingly critical ability to hold a surgical suture. Then we walk through the main fabrication strategies for getting collagen fibers to line up the right way: electrospinning, braiding, 3D bioprinting, core-shell designs, and hydrogel reinforcement. Each approach has its own strengths and trade-offs. Despite some encouraging results in animal studies, collagen scaffolds are not yet ready for regular clinical use. Three stubborn barriers stand in the way: poor vascularization means the inside of the scaffold stays starved of oxygen; incomplete remodeling leaves synthetic material behind long after it should be gone; and weak host integration keeps the scaffold from truly becoming part of the living tissue. We close by laying out the design principles we believe will finally push collagen-based scaffolds from the lab into the operating room.

Keywords: Collagen, Tissue Engineering, Scaffold, Tendon, Biomimetic Materials

1. Introduction

Tendon and ligament injuries constitute one of the most prevalent categories of musculoskeletal pathology, affecting millions of individuals annually across both athletic and general populations(1). The socioeconomic burden associated with these conditions is considerable, encompassing direct medical costs, lost productivity, and the frequently protracted rehabilitation periods required following surgical intervention. Tendons, which function to transmit contractile forces from muscle to bone, and ligaments, which stabilize joints by connecting osseous structures, are both composed predominantly of dense regular connective tissue with a highly specialized extracellular matrix (ECM) that confers exceptional tensile strength and fatigue resistance. Despite this mechanical sophistication, the cellular density and metabolic activity of these tissues are comparatively low, a feature that, whilst advantageous for sustained load bearing, fundamentally constrains their intrinsic regenerative capacity following injury (2).

The clinical implications of limited regenerative potential are profound. Spontaneously healing tendon tissue typically forms a fibrotic scar characterized by disorganized collagen deposition, altered crimp morphology, and inferior biomechanical properties compared with uninjured tissue(3). Histological examination of healed tendon reveals predominant expression of collagen type III rather than the collagen type I that dominates native tissue, together with hypercellularity and vascularization patterns that differ markedly from the norm (4). The functional consequences include reduced ultimate tensile strength, increased susceptibility to re-rupture, and impaired viscoelastic behavior that may compromise the tissue's ability to store and return elastic energy during locomotion(5). For massive rotator cuff tears, acute Achilles tendon ruptures, and anterior cruciate ligament (ACL) injuries, these limitations have driven the pursuit of tissue engineering strategies that might restore both the structural integrity and biological functionality of the injured tissue.

The central paradigm of tissue engineering involves the synergistic integration of scaffold architecture, cellular components, and bioactive signaling molecules to guide de novo tissue formation (6). Within this framework, scaffold design assumes particular importance for tendon and ligament applications because the engineered construct must not only provide a permissive environment for cellular infiltration and differentiation but also bear physiological mechanical loads from the moment of implantation through the extended period of tissue remodeling(7). Collagen, as the principal structural protein of native tendon ECM, represents a logical and biologically relevant scaffold material. Its inherent bioactivity, low immunogenicity when properly processed, and capacity for enzymatic degradation that parallels neo-tissue formation have established collagen as a favoured biomaterial for soft tissue regeneration(8).

The concept of bio-mimicry provides the intellectual foundation for scaffold design in tendon tissue engineering. Native tendon tissue exhibits a remarkable degree of hierarchical organization, with structural features spanning from the nanoscale arrangement of collagen triple helices to the macroscale bundling of fascicles into the complete tendon unit(9). A defining characteristic of this architecture is its pronounced anisotropy: collagen

fibers are aligned predominantly along the longitudinal axis of the tendon, an arrangement that enables efficient transmission of tensile forces whilst minimizing energy dissipation. This anisotropic organization is not merely a structural curiosity but is fundamentally linked to the mechanical function of the tissue, influencing cell morphology, differentiation, and ECM synthesis through mechanotransduction pathways (10, 11).

The recognition that scaffold topography profoundly influences cellular behavior has motivated extensive research into fabrication techniques capable of producing aligned collagen fiber scaffolds with controlled microarchitectural features. Aligned electrospun nanofibers, textile-braided fiber assemblies, and densely packed collagen yarns have all demonstrated capacity to direct cell alignment, upregulate tenogenic gene expression, and promote the deposition of organized ECM(12). Such scaffolds represent a significant advance over isotropic constructs, offering improved mechanical anisotropy and enhanced bio-instructive cues that more faithfully replicate the native tendon microenvironment.

This review provides a comprehensive critical appraisal of anisotropic collagen fiber scaffolds as biomimetic platforms for tendon and ligament regeneration. We systematically examine the hierarchical organization of native tendon tissue as the biological template for scaffold design, evaluate the principal fabrication strategies for engineering anisotropic collagen constructs, discuss the rationale and performance of hybrid hydrogel-fiber composites, and assess the emerging role of core-shell architectures in addressing the complexities of tendon-bone interface regeneration. Mechanical benchmarking against native tissue standards is presented, together with an analysis of the key challenges, including vascularization, long-term remodeling, and immune integration, that must be overcome to achieve successful clinical translation. Throughout, we emphasize the importance of mechanotransduction signaling, viscoelastic behavior, and the integration of multiple bio-instructive cues in guiding functional tissue regeneration.

2. Native Tendon and Ligament Microstructure

2.1 Hierarchical Organization of the Tendon Extracellular Matrix

A thorough understanding of native tendon microstructure is prerequisite to rational scaffold design, as the engineered construct must recapitulate the essential architectural and mechanical features of the biological template to guide appropriate cellular responses and restore functional load-bearing capacity. Tendon and ligament tissues exhibit one of the most highly ordered hierarchical structures in the vertebrate body, with organizational levels spanning approximately seven orders of magnitude in length scale(13). At the most fundamental level, individual collagen molecules, each comprising a triple helix of three polypeptide chains, assemble into quarter-staggered arrays to form collagen fibrils with characteristic 67 nm periodic banding patterns visible by electron microscopy(14). These fibrils, which range in diameter from approximately 50 to 300 nm depending on tissue age and mechanical demands, represent the primary load-bearing elements of the tendon ECM.

The next level of hierarchy involves the parallel bundling of collagen fibrils into collagen fibers (also termed primary fiber bundles or sub fascicles),

structures that typically range from 1 to 20μm in diameter and are bound together by the interfibrillar matrix composed predominantly of proteoglycans, glycoproteins, and interstitial collagen types(15). The proteoglycan decorin, in particular, has been identified as a critical regulator of fibril diameter and spacing, with knockout studies demonstrating significantly altered collagen fibril morphology and reduced tensile strength in decorin-deficient tendons(16). Other small leucine-rich proteoglycans including biglycan, fibromodulin, and lumican contribute to fibrillogenesis and the mechanical integrity of the interfibrillar matrix, whilst larger proteoglycans such as aggrecan and versican are concentrated at tendon compression sites and the tendon-bone interface(17, 18).

Multiple collagen fibers are subsequently bundled into fascicles (secondary bundles), which represent the fundamental structural and functional units of tendon tissue. Fascicles are typically 50 to 300 μm in diameter and are separated by the endotenon, a loose connective tissue layer containing blood vessels, lymphatics, and nerves that facilitates interfascicular sliding and provides the metabolic support required for fascicle maintenance(19). The endotenon is continuous with the epitenon, a dense connective tissue sheath that surrounds the entire tendon, and the paratenon, a loose areolar tissue that permits tendon gliding within the surrounding soft tissues. This multilayered sheath system is essential for tendon nutrition, particularly in regions where tendons are subjected to high friction or compression(20).

The hierarchical organization described above is not merely a structural feature but is intimately linked to the mechanical function of tendon tissue. The parallel alignment of collagen fibrils and fibers along the longitudinal axis of the tendon ensures that tensile loads are borne efficiently, with the stress-strain response of tendon tissue reflecting the sequential recruitment of collagen fibrils as the tissue elongates(21). The highly ordered hierarchical organization also contributes to the viscoelastic properties of tendon, with energy dissipation occurring through molecular rearrangements within the collagen triple helix, interfibrillar sliding mediated by proteoglycan-rich matrices, and the bulk flow of interstitial fluid(22). Table 1 delineates the

Table 1: summary of Hierarchical Organization. Both tissues follow a similar hierarchical pattern from nano to macro scale

Triple Helix (Nano)	Collagen Type I molecules (tropocollagen, ~1.5 nm diameter).
Microfibrils (Nano)	Aggregated triple helices staggered in pattern.
Subfibrils (Nano)	Bundles of microfibrils.
Fibrils (Micro)	Bundles of subfibrils (50–500 nm diameter). This is the key functional unit.
Fibers (Micro)	Bundles of fibrils (1–20 μm diameter).
Fascicles (Macro)	Bundles of fibers (visible to naked eye). Surrounded by endotenon.
Tendon/Ligament (Macro)	Entire structure. Surrounded by epitenon and outer paratenon (or synovial sheath in some regions).

hierarchical structural organization spanning from collagen to ligament

2.2 Crimp Patterns and Mechanical Anisotropy

A distinctive and functionally important feature of tendon collagen fibrils is the presence of a planar crimp or waviness pattern that is visible by polarised light microscopy and scanning electron microscopy (SEM). The crimp angle, which describes the amplitude of the wave-like undulation, varies between tendon types and anatomical locations but typically ranges from 5 to 20 degrees in unloaded tissue. This crimp morphology serves as a structural mechanism for accommodating physiological strains without subjecting collagen fibrils to excessive tensile stress. As tendon elongates under load, the crimp pattern progressively straightens through a process of geometric recruitment, with the toe region of the stress-strain curve corresponding directly to this crimp-flattening phenomenon(23). Only after the crimp has been fully eliminated do the collagen fibrils themselves experience significant axial strain, entering the linear elastic region of the mechanical response.

The functional significance of crimp extends beyond mere mechanical accommodation. Studies using small-angle X-ray scattering and confocal microscopy have demonstrated that crimp patterns are not uniform across a tendon cross-section but exhibit regional variations that may reflect differential mechanical loading histories(24). These observations have motivated interest in engineering scaffolds with crimped or wavy fiber architectures that might more faithfully replicate the native mechanical environment and guide appropriate tissue remodeling. The mechanical properties summarized in Table 2 vary substantially across anatomical sites. Consequently, a scaffold designed for one tendon or ligament cannot be assumed to perform adequately in another.

The anisotropy of tendon tissue extends beyond collagen alignment to encompass the orientation of cells, blood vessels, and proteoglycan distributions. Tenocytes, the predominant resident cell type, are elongated spindle-shaped cells that are aligned with the longitudinal axis of collagen fibers and extend cytoplasmic processes that contact adjacent cells through gap junctions, forming a three-dimensional

Table 2: Native Mechanical Demands by Anatomical Site

Tissue	Tensile Modulus (MPa)	Fatigue Life	Creep Strain	Suture Retention Force (N)
ACL	100-250	10^6–10^7	5–10%	50–80
Patellar tendon	300-500	10^7	2–5%	80–120
Rotator cuff	150-300	10^6	5–8%	40–70
Achilles	200-400	10^7	3–6%	60–100

communication network throughout the tendon volume(25).

2.3 The Tendon-Bone Interface: A Specialized Gradient Structure

The insertion of tendon into bone, termed the enthesis, represents a specialized anatomical structure that mediates the mechanical transmission of forces between two tissues with dramatically different material properties (25). The direct apposition of these dissimilar materials would create severe stress concentrations at the interface under physiological loading, predisposing to failure. zonal organization is characterized by gradients in collagen orientation, mineral content, and cellular phenotype. The tendon region adjacent to the enthesis contains highly aligned collagen type I fibers and fibroblast-like tenocytes. Progressing towards the bone, collagen fibers become increasingly interwoven with proteoglycan-rich matrix, and resident cells adopt a rounded fibro chondrocyte morphology with expression of cartilage-specific markers including collagen type II and aggrecan (26). The subsequent mineralized fibrocartilage zone contains hydroxyapatite deposits within the collagen matrix, with mineral content increasing progressively until full integration with the adjacent bone tissue is achieved. This graded structure effectively distributes mechanical stress across the interface, minimizing peak strains and enhancing the fatigue resistance of the attachment (27).

The complexity of the enthesis presents a significant challenge for tissue engineering approaches. Surgical repair of tendon-to-bone injuries, such as rotator cuff tears or ACL ruptures, typically results in the formation of a fibrovascular scar tissue interface rather than the regeneration of the native fibrocartilaginous insertion(28). This scar-mediated healing is associated with inferior mechanical fixation and a higher incidence of re-rupture, particularly under the high mechanical demand's characteristic of these anatomical sites. Consequently, scaffold designs that incorporate zonal gradients in composition, mineral content, and bioactive signaling to promote the regeneration of the native enthesis structure have emerged as a priority area for research.

3. Engineering Anisotropic Collagen Fiber Scaffolds

Native tendon and ligament possess hierarchical anisotropy from nanoscale fibrils to macroscopic fascicles. Here fabrication strategies of increasing architectural complexity are evaluated: aligned electrospinning, freeze-casting, three-dimensional bioprinting, and braided architectures.

3.1 Aligned Electrospinning

In electrospinning, aligned collagen fibers are essential for tendon and ligament regeneration because natural tenocytes sense and respond to topographic cues, aligning their actin cytoskeleton and depositing new collagen in the direction of fiber orientation, a process known as contact conduction (29). Electrospinning is suitable for mechanobiology studies, but is not suitable as a stand-alone load-bearing implant(30). Although, studies have shown that aligned fibers could limit tendon repair and cellular penetration is limited to 30–80 μm. However, Multilayer strategies can improve this properties(31).

3.2 Freeze-Casting

Cryo-casting, or ice templating, is a scaffold fabrication method based on the directional solidification of collagen suspensions along a controlled thermal gradient, followed by lyophilization to remove the ice phase and leave behind anisotropic, interconnected pore architectures(32). In contrast to electrospinning, which prioritizes nanofibrillar alignment and tensile load-bearing capacity, cryo-casting optimizes porosity and pore interconnectivity. The resulting scaffolds exhibit longitudinally oriented pores with diameters of 20–200 μm, supporting three-dimensional cellular infiltration and nutrient diffusion throughout centimeter-scale constructs(33). However, the absence of a continuous fibrous network limits unidirectional load transfer, as the discrete pore walls are prone to buckling under tensile stress. As a result, cryo-cast collagen scaffolds are best suited for applications requiring rapid host cell engraftment at the expense of immediate mechanical function. Thus, their utility is most evident in tissues such as tendon sheath grafts or non-load-bearing tissue interfaces—where biological regeneration is prioritized over structural strength.

3.3 Three-Dimensional Bioprinting

Bioprinting has emerged as a versatile regenerative strategy capable of producing patient-specific constructs that replicate the hierarchical organization of natural tendon tissue. Unlike conventional scaffold fabrication methods, 3D bioprinting allows for the deposition of cells and extracellular matrix (ECM) components, thereby allowing for the precise simulation of tendon-specific features such as anisotropic cell alignment, graded matrix composition, and region-specific mechanical properties. This level of control facilitates the engineering of constructs that not only mimic natural microstructure but also support directed ECM remodeling and tendon differentiation. Through the integration of bioinks- comprising hydrogels, natural and synthetic polymers, and decellularized ECM- researchers are engineering tendon constructs designed to emulate both the structural and functional properties of natural tissue(34). 3D bioprinting offers a unique capability that neither electrospinning nor freeze-casting can provide, namely graded anisotropy(35). A printed construct can be transformed from highly aligned parallel filaments that mimic the tendon matrix to randomly oriented filaments at the simulated junction. Cell-rich printing achieves high cell viability and rapid tendinogenic differentiation. Culturing under cyclic strain forces can improve the mechanical properties of the printed tissue. However, even then, the reported maximum modulus remains lower than that of natural tendon(36). A limitation of hydrogel-based printing methods is poor mechanical properties. The Young's modulus of printed samples is reported to be 0.1–5 MPa. Even after 14 days of cyclic straining, the maximum reported modulus reaches only 50–100 MPa(37).

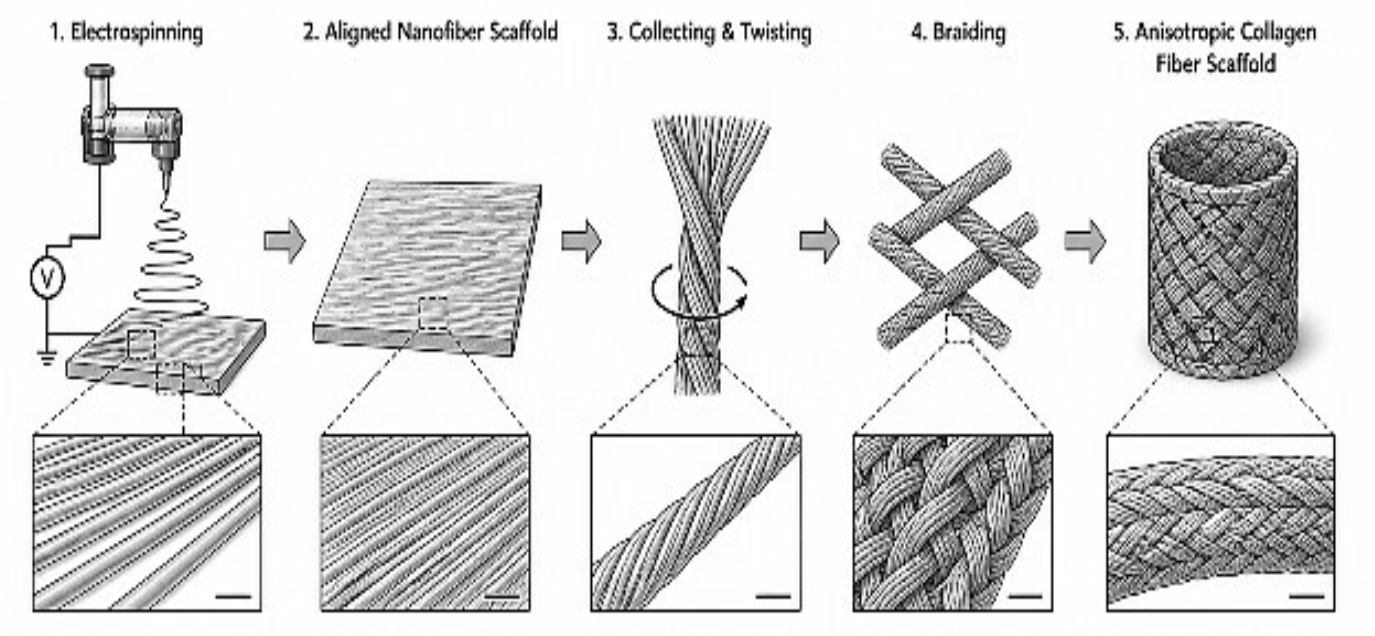
3.4 Braided Architectures

Native tendons possess a twisted, helical fascicular architecture that elegantly distributes tensile loads while allowing for vital inter-fascicular slippage. Braided scaffolds uniquely recapture this hierarchical design, weaving mesoscale yarn twists into macroscale patterns to mimic the native tissue’s biomechanical grace. While electrospun yarn braiding preserves the nanoscale alignment needed to

approach the lower bounds of native tendon strength application demands more(38). To overcome the inherent mechanical shortcomings of collagen, researchers have turned to hybridization with absorbable synthetic polymers—poly-L-lactic acid (PLLA) is a notable example. This strategy effectively bridges the mechanical gap and produces scaffolds that have the ability to be sutured to withstand forces during implantation and heal human-scale defects. (39).

However, mechanical strength is futile without biological integration .Woven scaffolds, like dense electrospun scaffolds, typically have limited pore dimensions that trap cells at the surface and prevent the cellular penetration necessary to weave the scaffold into living tissue within. An elegant solution is to weave the fibers inward and subsequently wash them out. This strategy dramatically expands the pore landscape, transforming a cell-free core into a suitable environment for deep tissue integration. This allows reparative cells to colonize the deep interior of the construct, transforming an inert structure into a living, healing tissue. The efficacy of this strategy is clear. According to a recent meta-analysis of preclinical models, woven collagen scaffolds consistently outperform other collagen-based approaches in facilitating functional recovery. However, their remarkable performance in animal studies has yet to be confirmed in human clinical trials and is considered a critical missing link in the ability to restore mobility to patients with tendon and ligament defects. Figure 1 compared design of align and braided fiber.

Figure 1: fabrication of braided anisotropic collagen scaffold. Align electrospun bundle are coupled and braided to introduce hierarchical crimp and bundle level anisotropy mimicking native tendon mechanic beyond simple align fiber design.



4. Hybrid Constructs: Hydrogel-Coated and Hydrogel-Infiltrated Collagen Fiber Scaffolds

Anisotropic collagen fiber scaffolds provide topographical guidance and mechanical support for tendon and ligament regeneration, yet they lack the bioactive microenvironment necessary for optimal cell infiltration, nutrient exchange, and controlled delivery of signaling molecules. To overcome this limitation, researchers have developed hybrid constructs that combine oriented collagen fibers with a hydrogel phase. Recent research highlights the promise of fiber-reinforced hydrogel composites for augmenting tendon and ligament repair and regeneration(40). These scaffolds provide both mechanical strength and a conducive microenvironment for biological processes required for connective tissue regeneration. There are two distinct integration strategies: (i) hydrogel-coated collagen fiber scaffolds, where a thin hydrogel layer covers the fiber surfaces, and (ii) hydrogel-infiltrated collagen fiber scaffolds, where the hydrogel fills the interfibrillar spaces throughout the entire scaffold volume.

4.1. Hydrogel-Coated Collagen Fiber Scaffolds

In hydrogel-coated constructs, aligned collagen fibers are first produced using some techniques like electrospinning, or etc. The hydrogel coating serves as a reservoir for bioactive molecules and biological cues (41). developed bioengineered living fibers by coating electrospun nanofiber scaffolds with cell -laden hydrogels encapsulating human adipose-derived stem cells (hASCs). Their scaffolds mimicked the native hierarchical structure of tendons and the size of tendon fascicles, with hASCs showing high elongation and cytoskeleton anisotropic organization typical of tenocytes. Importantly, the hydrogel layer acted not only as a hydrated biomimetic environment adequate for cell encapsulation but also as a carrier and delivery system for extracellular vehicles (EVs) to cells, improving their tenogenic differentiation. Furthermore, studies note that the bulk hydrogel component of a fiber-reinforced hydrogel composites can be comprised of natural materials such as collagen or fibrin, which generally allow for enhanced cell-mediated remodeling and better integration with the native tendon(42).

A critical concern is whether the soft hydrogel coating compromises the tensile performance of the collagen fibers. Fiber-reinforced hydrogel composites provide improved tensile strength, stiffness, and toughness compared to hydrogels alone. The incorporation of aligned fibers into these materials can mimic the aligned structure of native tendon tissue, accelerate tendon progenitor cell recruitment, promote tenogenic differentiation, and template aligned matrix deposition that reflects the organization of native tendon. In terms of in vivo performance, self-assembling peptide hydrogels have shown promising results. Another study on rabbit patellar tendon defects demonstrated that KI24RGDS peptide hydrogel implantation resulted in limited tendon elongation and better histological scores with uniformed collagen fiber orientation and early vascularization. The failure load of the patellar tendon was higher in the KI24RGDS group than that in the defect group, with no significant difference from intact patellar tendon at 8 weeks postoperatively(43).

4.2 Hydrogel-Infiltrated Collagen Fiber Scaffolds

In contrast to coating, infiltration aims to fill the entire void space between aligned collagen fibers with hydrogel. Fiber-reinforced hydrogel composites show great promise for achieving the biological goals of a tendon scaffold due to their highly tunable composition. In these scaffolds the fibrous component can be formed from a range of natural or synthetic materials, with innovative fabrication approaches including solution electrospinning (SES), melt electro writing (MEW), and melt blowing, enabling precise control over fiber geometry and mechanics. A major advantage of full infiltration is the dramatic improvement in permeability and mechanical integrity. Topographical features like fiber anisotropy and crimp of the fibrous component can be achieved either during fiber fabrication or during crosslinking of the composite material. In native tendon, the crimped morphology of collagen fibers confers tendon with a nonlinear stress-strain response and may protect fibers from mechanical damage.

The infiltrated hydrogel phase provides an ideal platform for sustained and localized drug delivery. Injectable nanofiber-hydrogel composite microparticles have been designed from cross-linked electrospun collagen nanofiber fragments surface-bonded to hyaluronic acid hydrogel networks. studies showed that these composites increased the overall storage modulus to a level comparable to native soft tissues while maintaining high porosity to allow host cell infiltration(44). Moreover, these nanofiber-hydrogel composite promoted macrophage/monocyte infiltration, migration, and spreading, enhanced the proangiogenic effect, and led to extensive tissue remodeling. Some studies compared fibrin versus collagen hydrogels for tendon tissue-engineered constructs and found that fibrin-based constructs exhibited improved tenogenic gene expression patterns, better cell-derived collagen alignment, and increased linear modulus compared with collagen-based constructs. In the context of tendon-bone healing after ACL reconstruction, KGN/PVA/n-HA composite hydrogel scaffolds have been successfully prepared and shown to promote ACL growth, collagen fiber formation, and effectively alleviate cartilage damage while preventing osteoarthritis occurrence (45, 46).

5. Core-Shell Collagen Scaffolds for Controlled Release and Zonal Regeneration

The native enthesis is a highly specialized transition zone that mitigates stress concentrations between the mechanically dissimilar environments of compliant tendon and rigid bone. Over a narrow spatial window of 500 μm to 1 mm, the tissue traverses four distinct zones creating a continuous gradient of both extracellular matrix composition and mineral content.(47) Recapitulating this abrupt yet continuous biophysical transition is critical for tendon tissue engineering; without it, surgical repairs suffer from mechanical mismatch and subsequent failure at the insertion site. However, recreating this multiphase gradient within a single biomaterial construct remains a formidable fabrication challenge, as it requires seamlessly integrating highly divergent cellular phenotypes and mechanical properties across a sub-millimeter scale (48).

Collagen-based core-shell architectures have emerged as a uniquely capable platform to address these dual biological and engineering hurdles. The core-shell topology provides discrete spatial compartments that enable the biomimetic patterning of the enthesis, allowing researchers to tailor the structural and mechanical properties of the core and shell independently to mimic adjacent tissue zones (49). Concurrently, these distinct compartments serve as localized reservoirs for the controlled, spatiotemporal release of bioactive molecules directing zone-specific cellular differentiation and matrix deposition. By unifying spatial gradient patterning with compartmentalized biochemical delivery within a collagen matrix, core-shell scaffolds provide the precise environmental cues necessary to drive the graded morphogenesis required for functional enthesis regeneration. (Figure 2).

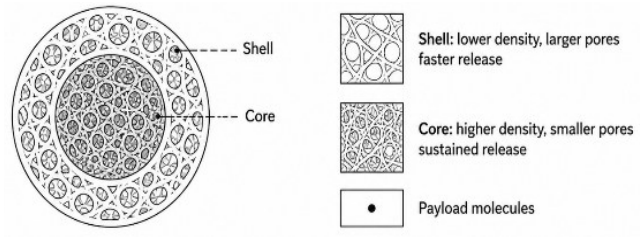


Figure 2: schematic cross section illustration of a core shell microfiber. The align collagen core (dark) confers mechanical strength and topographical cues for tenocyte alignment. The shell support cell adhesion, proliferation and nutrient exchange. The porous shell can be functionalized with biochemical signaling molecules to synergistically direct tenogenic differentiation and matrix remodeling.

5.1 Design Principles

At the heart of the design of collagen scaffolds for tendon repair lies an unavoidable biological compromise. On the one hand, the construct must be sufficiently dense and flexible to withstand physiological tensile forces immediately after implantation. On the other hand, it must remain sufficiently porous to allow for the penetration of tenocytes and allow for gradual matrix remodeling. Meeting both demands simultaneously is a major engineering challenge in this field.(50). Core-shell architectures get around this problem by separating the two functions. The inner core handles the mechanical load. It mimics the dense, highly aligned collagen fascicles found in the native tendon midsubstance, and often needs heavy crosslinking or synthetic reinforcement to hold sutures and withstand tension. The outer shell, in contrast, stays loose and bioactive. This protects the wound site while acting as a delivery depot for tendon-specific signals like GDF-5, recruiting cells and guiding organized matrix deposition.

But building these collagen core-shell constructs is where the real engineering difficulty lies. The fabrication method decides how faithfully the scaffold copies the tendon's natural hierarchy. Coaxial electrospinning produces continuous nanofibers between 300 and 1500 nm. That range beautifully matches the fine, aligned fibrillar texture that tenocytes depend on for sensing mechanical cues and elongating along the axis of strain. However, when the clinical goal calls for larger-scale structural transitions for instance, moving from core to shell over mm rather than µm coaxial bioprinting is usually the better choice(51). It deposits thicker, cell-laden collagen filaments (200–800 µm), giving

researchers the ability to print continuous spatial gradients, transitioning smoothly from a soft collagen core out to a mineralized shell. The simplest approach is sequential electrospinning or dip-coating, where a pre-formed tensile core is simply dipped into a collagen bath. While accessible, this method struggles with boundary control. As the wet collagen layers assemble, they tend to bleed into one another, blurring the interface. For a tissue like tendon that relies on strict mechanical and biochemical boundaries to function properly, that lack of spatial definition can ultimately limit the fidelity of the repair.

5.2 Controlled Release

Treating tendon injuries with growth factors has always been a race against time. When a traditional collagen scaffold simply soaks up these proteins the watery physiological environment quickly washes them out. Up to 80% of the payload can escape within the first 48 hours. This "burst release" not only wastes the therapeutic window but also fails to provide the sustained biochemical signaling that slow-healing tendons desperately need over weeks(7). Core-shell collagen scaffolds solve this by fundamentally changing how the payload is stored, wrapping the regenerative factors inside a protective physical barrier that forces the proteins to earn their exit.
The release kinetics are governed by the physical dimensions of this collagen architecture. By engineering a core diameter of 200–800 nanometers wrapped in a shell 50–200 nanometers thick, researchers create a strict diffusional bottleneck. In contrast, that same factor in a bulk-loaded collagen scaffold is largely gone before the tendon even begins to lay down new matrix.

Beyond just slowing down a single factor, this compartmentalization gives us spatial and temporal control over the entire healing timeline. Tendon repair isn't a single event; it requires different biological cues at different stages.(52) Because the core and shell are distinct reservoirs, we can segregate conflicting or complementary drugs. For example, loading the outer collagen shell with anti-inflammatory agents ensures they are released first to calm the post-injury inflammatory storm. Meanwhile, tucking tenogenic factors deep into the collagen core delays their release. By the time the shell's payload has diffused, the core's regenerative signals are just beginning to emerge, perfectly timing the transition from inflammation control to tendon rebuilding.

6. Mechanical Competence of Advanced Collagen Scaffolds

6.1 Native Tissue Benchmarks

Designing a scaffold for tendon or ligament repair requires confronting the demanding mechanical environment of the human body. These tissues are not simply strong; they are also remarkably heterogeneous and flexible, with their properties varying widely across anatomical locations, loading conditions, and even along the length of a single tendon. A scaffold that fails to account for this complexity is unlikely to be clinically successful. (53). Tensile properties vary widely across tendons and ligaments. The anterior cruciate ligament (ACL) exhibits moduli of 100–250 MPa and

ultimate strengths of 20–40 MPa. The patellar tendon, a biological powerhouse, operates at a substantially stiffer 300–500 MPa and 50–80 MPa. Rotator cuff tendons fall between these extremes. Such diversity demands that scaffold designs be tailored to the specific tissue being repaired, rather than adopting a one-size-fits-all approach. While the exact numbers vary depending on the anatomy, the baseline requirement is universal: over a lifetime, these tissues must endure millions of relentless loading cycles. Even the ACL, which operates at lower stress ranges than the patellar tendon, withstands thousands of cyclic loads every single day just from normal walking during athletic activity(54). A tendon or ligament scaffold must resist creep and cyclic degradation over millions of loading cycles, as even microscopic elongation can accumulate into clinical instability requiring surgical revision.

Yet, achieving this lifelong durability is only half the surgical battle. A scaffold must also survive the immediate trauma of the operating room. Suture retention is an essential but often neglected design criterion. A scaffold that fails to securely grip a surgical suture will detach from bone or tendon under intraoperative tension, rendering even optimal elasticity and cyclic durability clinically irrelevant. Even the most perfectly designed regenerative scaffold is useless if it detaches during early postoperative mobilization. Consequently, bridging the massive mechanical gap between what pure collagen can provide and what the active human body demands both in enduring millions of cycles and holding firm to a suture remains the central engineering hurdle in tissue regeneration.

6.2 Tensile Properties Across Fabrication Methods

The tensile properties of collagen scaffolds vary enormously with fabrication method, and a clear hierarchy emerges. Electrospun scaffolds, despite their excellent nanoscale alignment, are mechanically weak due to discontinuous fibers and limited load transfer at fusion points(55). Freeze-cast scaffolds fare even worse. Their fragile, thin pore walls tend to buckle and collapse under tension rather than bear the load, leaving them with a meager modulus of 1–10 MPa. Then there's bioprinting, which starts at the absolute bottom of the mechanical ladder. Fresh off the printer, these constructs are essentially soft hydrogels, offering moduli of just 0.1–5 MPa(56).

It's a delicate balancing act between giving the body the mechanical support it needs immediately and ensuring the biology can catch up before that temporary scaffolding disappears.

6.3 Fatigue Resistance and Cyclic Loading Performance

Tendons and ligaments rarely snap from a single, massive pull; they break down because their collagen matrix accumulates fatigue damage from millions of repetitive steps. Collagen scaffolds for tendon repair must resist two distinct cyclic failure mechanisms: fatigue fracture and creep. Fatigue fracture results from the stepwise accumulation of microscopic fiber damage under repeated load, leading eventually to sudden, complete rupture.(57). Aligned electrospun collagen mats,

while excellent for studying how tenocytes respond to mechanics, are highly vulnerable to this. At just 20% of their maximum strength, they survive only 10,000 to 100,000 cycles far short of the one million cycles required to reconstruct a human anterior cruciate ligament (ACL). Braided collagen scaffolds perform much better because their architecture mimics the load-sharing of native tendon fascicles, with some hybrid designs surviving several million cycles(58, 59). Yet, they aren't perfect; just as natural collagen fibers can fray over time, braided scaffolds suffer gradual degradation from internal fiber-on-fiber abrasion.

Creep is the permanent stretching of a material under a constant load. If a scaffold creeps too much, the reconstructed tendon gradually lengthens, leaving the joint chronically loose and unstable. The native ACL is a masterclass in creep resistance, stretching less than 3% even after a million cycles, thanks to its tightly crosslinked collagen architecture(60). Electrospun collagen scaffolds cannot replicate this; because their individual fibers slide past one another under tension, they stretch by an unacceptable 5 to 15%. Braiding the collagen locks the fibers together, cutting creep down to 3–8%. When synthetic fibers are braided alongside the collagen in hybrid designs, creep drops below 2%, perfectly matching native tissue but only while those synthetic fibers remain intact. Once they dissolve, the load shifts entirely to the remaining collagen and whatever new tissue the body has built, causing creep values to rise again(61). This highlights a crucial reality for tendon engineering: a scaffold's ability to endure millions of cycles without stretching out of shape is far more predictive of clinical success than its static pull strength, making fatigue testing an absolute necessity for evaluating new collagen biomaterials.

6.4 Suture Retention and Saturability

Suture retention is a practical necessity that doesn't get enough attention in biomaterials research. Electrospun collagen mats tear under minimal tension making them incredibly frustrating to handle in the operating room. Braided scaffolds, on the other hand, mechanically interlock with sutures. Pure braided collagen achieves pull-out strengths of 4 to 8 Newtons, while hybrid braids hit 8 to 15 Newtons. Given that the bare minimum for human tendon repair is around 10 Newtons, hybrid braids are often the only constructs that cross that surgical threshold (62)

However, pushing these scaffolds to clinical strength brings us to a critical concept: saturability. Collagen, by its very nature, has a mechanical ceiling. Even with perfect fiber alignment and maximum crosslinking, pure collagen can only get so strong. Adding synthetic fibers helps us break through that ceiling, but this too has a point of diminishing returns. The sweet spot for hybrid scaffolds is between 20% and 40% synthetic material by volume(63). Push beyond that, and you gain almost no additional mechanical advantage, while actively diluting the biological cues that make collagen so valuable for tissue regeneration. The same principle applies to crosslinking—there is an optimal window. Push past it, and the scaffold becomes brittle, completely undermining its fatigue life. Ultimately,

smart scaffold design means respecting these natural limits.

7. Challenges in Clinical Translation

Despite encouraging results in animal models, the leap to clinical application has been difficult. Among the main obstacles are: insufficient angiogenesis, which deprives the scaffold core of oxygen and nutrients; incomplete regeneration, which prevents the gradual replacement of the synthetic material with functional host tissue; and poor integration with the host, in which the construct does not fully integrate with the surrounding biological environment .One of the challenges in tendon engineering is keeping the center of a thick collagen scaffold alive. Tendons are naturally poorly vascularized tissues, and when a cell-free collagen scaffold exceeds 2 millimeters in diameter, it almost inevitably develops a dead, acellular core. researchers are trying to jumpstart blood flow into the scaffold(64). Pre-seeding collagen scaffolds with endothelial cells builds a miniature vascular network before the scaffold is even implanted. Once placed in the body, this network plugs directly into the patient's own bloodstream within just 3 to 5 days, leading to uniform cell survival and tissue growth in rat model(65). Flooding the repair site with too many blood vessels risks creating hypervascularity, disorganized scar tissue that lacks the mechanical strength of a healthy tendon. A more structural solution lies in the physical design of the collagen matrix itself. By engineering the collagen scaffold with pore architectures exceeding 100 µm, we give invading capillaries the physical space they need to migrate into the construct naturally, offering a better balance between getting the nutrients in and keeping the tendon's fibrous integrity intact.

The scaffold-native tissue interface is mechanically the weakest point. In preclinical studies, 68% of mechanical failures occurred at the scaffold-native tendon interface. Three strategies improve integration (66)

Future Perspectives

The development of gradient scaffolds that exhibit a gradual transition in properties from the bone region (enthesis) to the tendon region, thereby mimicking the native tissue interface. Dynamic tension bioreactors should be employed to culture scaffolds seeded with diseased cells under cyclic mechanical stimulation that replicates physiological movements prior to implantation. Additionally, cell-free scaffolds functionalized with chemotactic peptides could be designed to attract the host's endogenous stem cells to the lesion site, promoting in situ regeneration. Four major directions will shape the next decade. First, resolving the anisotropy-porosity paradox requires multi-step fabrication creating dense aligned scaffolds followed by controlled macroporosity generation. Second, dynamic mechanical conditioning integrated into scaffold fabrication using bioreactors could increase modulus 2-5-fold. Third, engineering vascularization into thick scaffolds demands adaptation of sacrificial writing, bioprinting of vascular channels, and perfusable networks. Fourth, clinically relevant large animal models with aged or comorbidity-modified animals are required for regulatory approval.

Conclusion

Anisotropic collagen scaffolds have advanced substantially, but anisotropy alone is insufficient for functional tendon regeneration. Braided architectures best meet the mechanical requirements of load-bearing repair, achieving tensile moduli of 150–350 MPa and strengths of 30–60 MPa when combined with 20–40% synthetic polymer, though fatigue resistance exceeding one million cycles without creep remains unachieved. Core-shell designs enable controlled release and zonal regeneration but add complexity without proven clinical benefit in large animals; the tendon-to-bone enthesis represents the most compelling application for this technology. Vascularization, remodeling, and host integration are the interdependent rate-limiting steps for translation, and no solution has been validated in human-sized defects. The field must move beyond rodent models to rigorous large animal studies recapitulating human anatomy and healing capacity. With continued progress addressing these challenges, the first anisotropic collagen scaffold for human tendon or ligament reconstruction could reach clinical trials within 5-10 years.

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