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REVIEW

Artificial Single-Layer, Multi-Layer, and Gradient Scaffolds for Enhancing the Healing of Tendon-to-Bone Interfaces: A Mini-Review

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Abstract: Tendon healing after ligament or tendon reconstruction remains a significant challenge. Regenerative tissue engineering, an interdisciplinary field that combines biology, materials science, and engineering, offers promising solutions. Recent developments have introduced scaffold materials designed to enhance the proliferation and differentiation of tendon-to-bone tissue cells. These scaffolds possessing three-dimensional composites of tissue cells and biomaterials, have proven effective in facilitating tendon-to-bone curing post-surgery. The successful development of the tendon-to-bone interface is a critical factor for early rehabilitation and functional recovery. In this mini-review, we present a comprehensive update on contemporary strategies for synthetic scaffold-based materials and their influence on tendon-to-bone healing. We described the synthetic materials compositions, structures and features of single-layer, multi-layer, and gradient scaffolds with their special mechanical properties. We examined the construction of engineering scaffolds from the perspectives of biomaterials and design strategies, providing a comprehensive evaluation of the advantages and disadvantages associated with each approach. Ultimately, this review articulates clear research directions aimed at achieving breakthroughs in future studies.

Keywords: tendon healing, regenerative tissue engineering, synthetic scaffold materials

Introduction

Rotator cuff tears (RCTs), anterior cruciate ligament (ACL) injuries, and Achilles tendon (AT) ruptures are among the most common ligament and tendon injuries in sports medicine.[1] Due to their complex structural requirements, these injuries often necessitate reconstruction of the tendon-to-bone interface, typically through the implantation of an artificial tendon.[2] The effectiveness and prognosis of such procedures depend significantly on the successful healing of this interface, as surgical treatment alone frequently falls short.[3]

Advancements in tissue engineering have demonstrated the promise of engineered scaffolds in enhancing tendon-to-bone healing.[4] This field integrates cells with bioactive materials to form cell-biomaterial complexes, which can be implanted either in vivo or in vitro for the purpose of repairing and regenerating damaged tissues and organs.[5] Tissue-engineered bionic scaffolds are three-dimensional structures made from tissue cells, bioactive factors, and scaffold materials, designed to be implanted into injured ligaments or tendons to restore their anatomical and functional integrity.[6] Recently, an increasing amount of attention has been directed towards a series of growth factors (GFs), primarily including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF). This focus also encompasses their delivery methods, techniques for scaffold construction, and strategies that integrate scaffolds, cells, and GFs. Tissue engineering scaffolds for tendon-to-bone healing are generally classified into two categories: bio-derived scaffolds (such as a cellular extracellular matrix

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(ECM) scaffolds) and synthetic scaffolds.[7] Nevertheless, we still lack some perspectives that can integrate natural structures, characteristics, and engineering strategies. Although scaffold construction methods with significant importance in mechanical property recovery have received much attention, there are few reviews specifically focused on this area due to it being the most challenging part of tendon-to-bone regeneration.Furthermore, the absence of a comprehensive overview of the challenges and future perspectives in this field also diminishes the motivation of new researchers to engage in this area.

This review initially examines the composition, microstructure, essential bioactive factors, and mechanical properties of various significant tendons in synthetic scaffolds. Subsequently, it summarizes the research advancements in scaffold-based tissue engineering, highlighting promising biomaterials, advanced techniques, and innovative designs. Finally, the current challenges and future perspectives within this field are discussed.

Structure and Importance of the Tendon-to-Bone Interface

Anatomical Structure of the Tendon-to-Bone Interface

Under normal physiological conditions, tendon-to-bone interfaces typically feature a four-layer transitional structure. Here, collagen fibers from the tendon gradually spread and merge with bone fibers, as observed at the femoral insertion of the ACL and the humeral insertion of the supraspinatus tendon. This layered transition effectively distributes stress across the tendon-to-bone junction, thereby minimizing stress concentration and reducing the risk of separation. Conversely, some tendon-to-bone interfaces lack this transitional structure, resulting in tendons or ligaments attaching directly to the bone. Some reviews have provided a comprehensive summary of the natural structure and functions of enthesis tissue, as well as the factors influencing the development or healing of specific tendon-to-bone interfaces. Additionally, they have outlined the criteria pertinent to tissue engineering.[8] The processes involved in forming these interfaces and their functional implications are not yet fully understood.

Cellular and Molecular Composition of the Tendon-to-Bone Interface

From a microscopic perspective, the cellular and extracellular matrix compositions at various regions of the tendon-to-bone interface exhibit significant variations. Specifically, the fibrocartilage zones at the tendon ends differ markedly from the central interface region. At the molecular level, the tendon and bone ends are rich in type I collagen, with the bone also featuring significant calcium salt deposits. In contrast, the fibrocartilage zone is dominated by type II collagen and a matrix abundant in proteoglycans.[9] Both the tendon and fibrocartilage regions also contain substantial amounts of leucine-rich proteins, which are thought to facilitate the divergence of collagen fibers at the tendon ends.

In terms of cellular composition, the tendon end primarily houses fibroblast-like tendon cells. The fibrocartilage band consists mainly of fibrocartilage cells that enlarge with calcium deposition. The bone end comprises osteoblasts, osteocytes, and osteoclasts.[10]

Importance of Restoring the Tendon-to-Bone Interface

Restoring the tendon-to-bone interface through surgery alone is challenging due to the significant differences in cellular and ECM compositions between soft and hard tissues at the interface. Surgical reconstruction often leads to reactive scar tissue rather than a true restoration of the natural interface.[11] This scar tissue commonly suffers from issues such as fat infiltration, disorganized fiber alignment, diminished elasticity, and reduced tensile strength. Repeated stress on the tendon or ligament can cause further microscopic damage or structural failure within the scar, leading to localized edema, aseptic inflammation, pain, and potentially surgical failure or detachment of the tendon-bone interface. Therefore, the advancement of enhanced techniques for tendon-to-bone healing holds significant research and clinical relevance.[12]

Synthetic Scaffolds for Tendon-to-Bone Healing

The ideal scaffold materials include comprehensive performance, for example, its' biodegradability and degradation rate suitable for the growth rate of tissue; three-dimensional structure and 80% porosity; good compatibility, non-immunogenic to the surrounding tissues; good surface activity, suitable for adhesion, and provide a good

microenvironment; as well as plasticity, the structure of the scaffold plasticized and unchanged. Tissue engineering scaffolds function as carriers for stem cells, growth factors, or nutrients, improving the repair environment and directing cell distribution and differentiation through their structural design.[13] This method enhances tendon-to-bone healing by influencing how repair cells differentiate. Although bio-derived scaffolds show excellent performance, their application is limited by issues such as scarce availability, high cost, and challenges in processing living tissues.[14] Conversely, most of the synthetic polymer materials adopt the concept of biomimicry to synthesize polymer materials to replace extracellular matrix, and their main advantages are wide sources, strong plasticity, and better induction and promotion of chondrocyte adherence, proliferation and differentiation. These synthetic scaffolds, which are more accessible and affordable, have emerged as a key area of research for tendon and bone repair. They are typically classified into three categories based on their structure: single-phase, polyphase integrated, and gradient biomimetic scaffolds.[15]

Criteria for Selecting Synthetic Scaffold Materials

Tendon-to-bone fixation methods are primarily classified into anchor suture techniques and transosseous suture methods. A representative example is the reconstruction of the rotator cuff supraspinatus insertion.[16] The substantial tissue gap created during this procedure complicates the secure fixation of scaffold materials using traditional interfacial filling scaffolds (Figure 1A). As a result, mesh-bridging scaffolds (Figure 1B), made from artificial polymers with both mechanical strength and biodegradability, are commonly used. These scaffolds provide essential support, distribute tensile stress at the interface, and can be loaded with growth factors and other active substances to guide repair cell behavior.[17] In contrast, the transosseous tunnel technique, frequently used for anterior cruciate ligament reconstruction, involves a narrower space between the bone tunnel and the reconstructed ligament. In this context, interface-filling scaffolds (Figure 1C) are preferred. These scaffolds, composed of natural, degradable, and non-toxic polymers, gradually break down to avoid obstructing tendon-to-bone integration. Additionally, ECM components such as collagen and hydroxyapatite are often added to improve integration.[18]

Single-Layer Scaffolds

Studies on single-layer scaffolds began early and was initially extensive, focusing on easily degradable materials such as gelatin. These scaffolds were designed to release nutrients as they degraded.[19] For instance, Huang et al's work with gelatin scaffolds embedded with simvastatin and hydroxyapatite nanoparticles (na-HAP) showed that scaffold degradation could enhance the proliferation and differentiation of rat bone marrow mesenchymal stem cells (BMSCs), thereby supporting

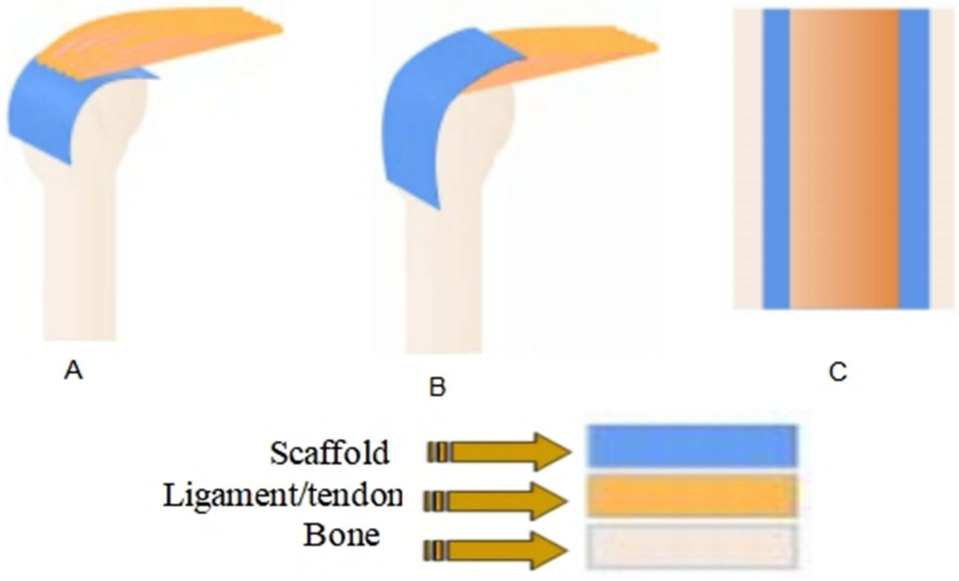

Figure 1 Tendon-to-bone fixation methods (**A**)The substantial tissue gap using traditional interfacial filling scaffolds (**B**) mesh-bridging scaffolds with both mechanical strength and biodegradability (**C**)Interface-filling scaffolds.

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tendon-to-bone healing.[20] However, it became apparent that these degradable materials lacked sufficient mechanical strength, leading to deformation or rupture after implantation. Such weaknesses created discrepancies between in vivo and in vitro findings and could hinder local healing.[21] To address these limitations, researchers have developed scaffolds from more robust and biocompatible materials, such as polycaprolactone (PCL) and polylactic acid-glycolic acid (PLGA). These materials are less likely to deform, offer prolonged slow release, and better support repair cell growth.[22] For example, Reifenrath et al created a chitosan-coated PCL fiber scaffold that released TGF-β, facilitating the development of fibrochondroid tissue at the tendon-to-bone interface, thereby enhancing tendon-to-bone healing.[23] Kempfert et al employed a 3D-printed titanium alloy microporous scaffold loaded with transforming growth factor-β3 (TGF-β3), which effectively encouraged new bone formation through sustained release of TGF-β3.[24] Zhu et al developed a PCL scaffold with kartogenin (KGN), which was designed to release KGN gradually, supporting cartilage formation and collagen alignment, and thus enhancing the mechanical strength of the healed area.[25] Overall, single-layer scaffolds made from PCL combine biodegradability with superior mechanical strength, preventing occlusion of the tendon-to-bone interface and promoting effective healing.[26]

Single-layer scaffolds, especially mesh-type bridge scaffolds, are essential in tendon-to-bone healing. They disperse nutrients, provide mechanical support, and serve as barriers to prevent undesirable tissue growth such as scar tissue and fat. Kim et al created a PCL/propylene glycol and ethylene oxide polymer patch scaffold embedded with platelet-derived growth factor and bone morphogenetic protein 2. The scaffold's mesh structure ensures controlled growth factor release and prevents fibrous tissue infiltration at the repair site. Animal studies suggest that this scaffold effectively supports tissue regeneration similar to the original tendon-to-bone junction.[27]

Nevertheless, the large tissue gap at the healing site can cause released nutrients to spread to unintended areas, potentially leading to adverse effects. Recent research has focused on scaffolds with specialized topological structures to address this issue. These scaffolds, with parallel or channel-like arrangements, guide tendon and osteogenic differentiation through anisotropic porous networks. For example, Chen et al developed a PLGA scaffold with a randomly arranged porous structure that supports BMSCs and enhances repair at the tendon-to-bone interface.[28] Similarly, Chen P et al's polyethylene glycol (PEG)-PCL/45S5 bioactive glass composite scaffold features a parallel channel structure that optimizes fibrocartilaginous collagen alignment. Scaffolds with these engineered structures offer superior mechanical strength, elasticity, and toughness. They create a conducive environment for cell adhesion and growth, support the unhealed tendon-to-bone interface, and reduce the risk of recurrence and fracture. Research on single-layer scaffolds has progressed significantly, focusing on improving the healing microenvironment, enriching repair cells, and regulating their growth and differentiation. Their versatility and integrity allow for customization to fit irregular repair sites, making them highly effective for various tendon-to-bone healing applications.[29]

Multi-Layer Scaffolds

The metabolic and proliferative needs of chondrocytes and osteoblasts challenge single-layer scaffolds, which often struggle to support osteogenesis, chondrogenesis, and tendon formation simultaneously. To overcome these limitations, multi-layer integrated scaffolds have been developed. These scaffolds employ a multi-layer structure, each layer providing a specific function to create optimized microenvironments for the cells at both ends of the interface. Their designs vary, with some scaffolds focusing on providing space for cell attachment and growth, thereby bridging the repair site effectively. Romeo et al introduced a pioneering double-layered scaffold made of polyglycolic acid and poly-L-lactide-co-ε-caprolactone, which was the first scaffold specifically approved by the FDA for tendon-to-bone healing. Animal studies demonstrated that this scaffold facilitated the formation of a transition zone analogous to the natural tendon-to-bone junction. Clinical trials further showed a 91% healing rate for RCTs repairs, with no reported adverse events.[30]

In another advancement, Alkaissy et al developed a multi-layer integrated scaffold incorporating electrospun PCL and polydioxanone (PDO) filaments into a 3D-printed PCL base.[31] This scaffold, with its dual soft and hard phases, effectively addresses tissue defects and supports cell reconstruction at the tendon-to-bone interface. Its stable, non-toxic properties and robust mechanical strength make it a promising option for clinical use, offering reduced risk of immune rejection and ensuring stability after implantation. Recent research has advanced the integration of biochemical signals, such as growth factors and nutrients, into multi-layer scaffolds to improve cellular enrichment and regulate cellular behavior. For example, Tarafder used 3D printing to fabricate scaffolds from PCL and PLGA, embedding layers with CTGF, TGF-β3, and bone morphogenetic protein-2 (BMP-2).[32] This design enables the sequential release of CTGF for tendon regeneration, BMP-2 for bone formation,

and CTGF plus TGF-β3 for cartilage development, thereby more effectively recreating the natural tendon-to-bone interface. Despite these advancements, controlling the spatial and temporal release of growth factors remains challenging. Uncontrolled release could lead to ectopic tissue growth or unintended effects elsewhere in the body. To mitigate this, researchers are exploring the use of ECM components and designing topological structures to better direct cell differentiation. Cong et al developed a three-layer scaffold using electrospinning technology. This scaffold features type I collagen/PCL fibers arranged in parallel at one end, type II collagen/PCL fibers in a non-oriented arrangement in the middle, and hydroxyapatite nanoparticles/PCL fibers at the other end, simulating the natural tendon-to-bone matrix and promoting the formation of transitional structures in vitro.[33] Similarly, Li et al created a three-layer scaffold using 3D printing with PCL and tricalcium phosphate (TCP). Animal studies showed that this scaffold supported the formation of transitional structures with calcified cartilage bands.[34] Although multi-layer scaffolds provide a more comprehensive approach to tendon-to-bone healing than single-layer scaffolds, they face challenges such as diminished structural integrity and inconsistent degradation rates among layers. Addressing these issues—by optimizing component interactions and managing degradation rates—is essential for enhancing the clinical effectiveness of multi-layer scaffolds.[10]

Biomimetic Gradient Scaffolds

Although multi-layer integrated scaffolds simulate the layered structure of the natural tendon-to-bone interface, they often fall short of replicating its continuous and transitional nature. To overcome this limitation, biomimetic gradient scaffolds have been developed to incorporate a gradual transition of ECM components. For instance, applying a PLA solution to the surface of polylactic acid/na-HAP patch scaffolds induces swelling and diffusion at the solid-liquid interface, creating a gradient in na-HAP concentration. Experimental results show that adipose-derived mesenchymal stem cells seeded on these scaffolds demonstrate region-specific differentiation. Similarly, a study with fibroin scaffolds immersed in simulated body fluids revealed gradient calcium deposition.[35] This calcium gradient influenced the differentiation of BMSCs, corresponding to the gradient of calcium deposition. These gradient scaffolds are designed to regulate cell differentiation through variable calcium deposition, reproducing the structure and function of the natural tendon-to-bone interface. This approach is essential for facilitating effective tendon-to-bone healing. Future research should focus on integrating specific topological structures into gradient biomimetic scaffolds to further enhance their ability to regulate cellular behavior. Cinici et al developed a hydrogel scaffold using a gradient of na-HAP concentration and a parallel gelatin microstrip structure that optimizes collagen fiber alignment in the ECM.[36] Zhu et al created a three-dimensional HAP/PLGA scaffold using thermally induced phase separation technology, which features graded calcium deposits and a parallel channel-like structure for tendon cell growth, along with a porous structure supporting bone cell growth. This design closely emulates the structure and function of the natural tendon-to-bone interface and has shown significant potential for improving tendon-to-bone healing. Animal studies confirm that these gradient biomimetic scaffolds effectively promote tissue formation resembling the natural tendon-to-bone interface and improve the tensile strength at the repair site.[37] The gradual transition in ECM components supports differential cell differentiation, reducing tissue discontinuity and strengthening the healed tendon-to-bone interface (Figure 2).

Gavinho et al advanced scaffold technology by integrating poly(lactic acid) (PL) into the electrospinning solution, creating a transition from anisotropic to isotropic na-HAP threads. This innovation produced a three-dimensional scaffold with a gradient in ECM components and a continuously varying topological structure. Experimental results demonstrated that human adipose-derived mesenchymal stem cells (hADMSCs) cultured on this scaffold exhibited significantly greater ECM calcification and osteogenic differentiation compared to control groups without scaffolding. This gradient biomimetic scaffold effectively replicates the natural tendon-to-bone interface, enhancing healing outcomes.[38,39] Its seamless gradient structure, lacking internal layered interfaces, offers superior mechanical properties compared to traditional multi-layer scaffolds. As a result, it is considered an ideal material for tendon-to-bone repair and is a key focus in ongoing research.[40,41,] Future studies should further investigate the scaffold's composition, structure, and phenotypic effects, while also aiming to streamline the fabrication process.[4,42,43]

Conclusions and Future Perspectives

Numerous synthetic scaffolds have been developed to effectively promote tendon-to-bone healing. After thorough sorting and analysis, it has been observed that many studies (such as those involving GFs and platelet-rich plasma) have yielded promising

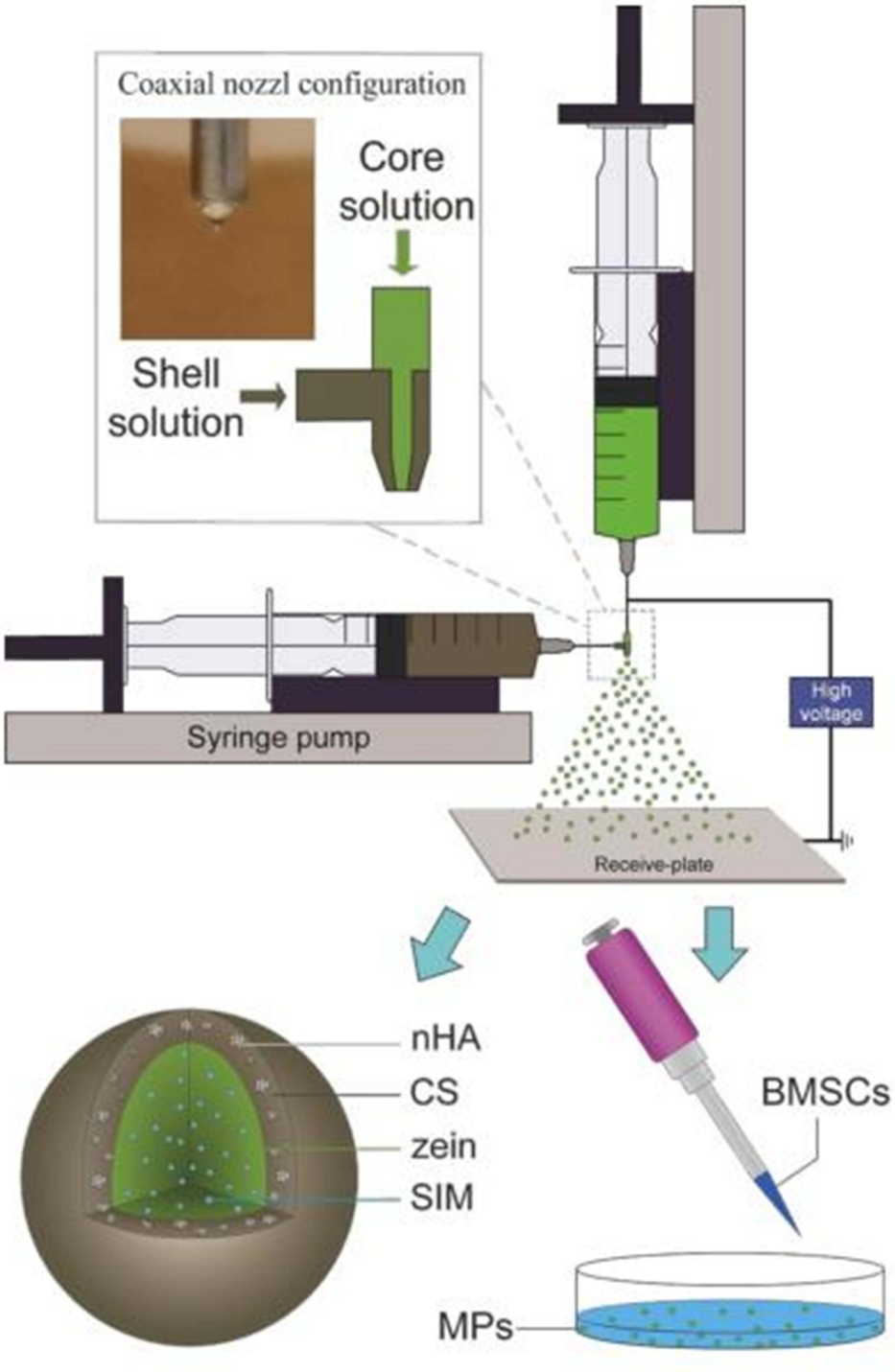

Figure 2 ECM components transition with differential cell differentiation to strengthen the tendon-to-bone interface.

results in enhancing tendon and bone healing. However, many of these techniques remain at the animal experimentation stage, and there is currently no established standard for the specific mechanisms, timing, or dosages of action (Table 1). Given that this repair process involves both tendon stem cells and BMSCs, research on synthetic scaffolds should concentrate on two key areas. First, efforts should aim to enhance the mechanical strength of these scaffolds, reduce production costs, and standardize fabrication processes to improve their practical application. Second, innovation in scaffold design should incorporate diverse signals, including biochemical (eg, growth factors and KGN), physical (eg, localized fluid shear stresses), and geometric (eg,

Table 1 Overview of Classification and Characteristics of the Artificial Scaffolds

Scaffold Types	Synthetic	Biological	Hybrid	Ref
Single-layer	Gelatin methacryloyl (GelMA), a promising biomaterial for engineering scaffolds.1	Kartogenin (KGN) promotes selective differentiation of bone marrow mesenchymal stem cells (BMSCs).	KGN-loaded GelMA hydrogel scaffolds possessed the fibrous structure, oriented fibrocartilage formation.	[20]
Single-layer	Polycaprolactone (PCL), an important polymer with a large range of biodegradability.3	KGN-loaded PCL (KGN-PCL) membranes significantly stimulated chondrogenic and tenogenic differentiation of marrow stromal cells.	KGN-PCL membranes possessed the fibrous structure, oriented marrow stromal cells.	[25]
Single-layer	PCL/Pluronic F127 membrane, a promising combined biomaterial with selective permeability, hydrophilicity and osteoconductivity.	Dual growth factors include (platelet-derived growth factor-BB [PDGF-BB] and bone morphogenetic protein-2 [BMP-2]).	PDGF-BB and BMP-2-immobilized polycaprolactone (PCL)/Pluronic F127 asymmetrically porous membrane, possessed the sponge structure and continuously released both growth factors and their complementary effect to create a multiphasic structure like a native structure.	[28]
Multi-layer	PCL/Polydioxanone (PDO), a biphasic materials consisting of soft and hard components, which can mimic this interface.	No bio-active substance.	The combining electrospinning and 3D printing biphasic scaffold components possessed the sponge structure, were noncytotoxic, tendon and bone cells could be grown on the cuff and block, respectively.	[31]
Multi-layer	PCL/poly (lactic cogly -colic acid) (PLGA), a biphasic materials consisting of soft and hard components, which can mimic this interface.	Design of 3D-printed scaffolds with spatiotemporal delivery of connective tissue growth factor (CTGF), transforming growth factor beta 3 (TGF, β3) and BMP2.	A micro-precise spatiotemporal delivery system embedded in three-dimensional (3D)-printed scaffolds, possessed the sponge structure, enabled the delivery of multiple GFs.	[32]
Gradient layer	An aligned gelatin microribbon (μRB) hydrogel scaffold with hydroxyapatite nanoparticle (HA-np) gradient for guiding zonal-specific differentiation of human mesenchymal stem cell (hMSC) to mimic the bone-tendon interface.	No bio-active substance.	Aligned gelatin μRBs with gradient cues of hydroxyapatite nanoparticles (HA-np) as 3D scaffolds, possessed the sponge structure, oriented zonal-specific differentiation of hMSCs to mimic the bone–tendon interface.	[35]
Gradient layer	An anisotropic yarns (A-Yarns) and isotropic threads with nanohydroxyapatite (I-Threads/ PL@nHAp).	Platelet lysate (PL).	A-Yarns/PL were fabricated to recreate the tendon- and bone-micro structures and both incorporated with PL using emulsion electrospinning, possessed the sponge structure, sustained and local delivery of growth factors, cytokines and chemokines.	[36]
Commercially available	An interposition electrospun nanofiber scaffold composed of polyglycolic acid (PGA) and poly-L-lactide-co-ε-caprolactone (PLCL).	No bio-active substance.	The PGA-PLCL nanofiber scaffold possessed the fiber structure, enabled collagen fiber integration into bone without scar interposition.	[30]

oriented fiber arrangements for tendon-like tissue regeneration) signals, as well as surface curvature. These strategies are designed to more accurately replicate the physiological tendon-to-bone interface, effectively guide and regulate stem cell behavior, and ultimately support the structural repair of this interface.

Data Sharing Statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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