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3D Bioprinting of Patient-Specific Tendon/Ligament Grafts: Biomechanical Challenges and Clinical Translation

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ABSTRACT

Musculoskeletal injuries of tendons and ligaments pose a clinical challenge that is most intricate because of the inherent slow healing rate and the multilayered structure of these tissues. Stable repair techniques, such as autografts and allografts, are often constrained by the morbidity of the donor site, its limited availability, and immunological rejection possibilities. Three-dimensional (3D) bioprinting is recognized as a paradigm shift, which promises the possibility to print patient-specific grafts reflecting the anatomy and physiology of the site of the injury with a high level of accuracy. Using combined biological inks like decellularised extracellular matrix (dECM) and synthetic polymers, scientists can now engineer constructs that promote regenerative, but not merely reparative, healing. There are, however, major challenges such as the implication of the extreme mechanical anisotropy of natural tissues, smooth integration in the tendon to bone interface (enthesis) and navigation of the complex regulatory cascades to clinical practice. With approximately 200,000 ACL-related injuries occurring annually in the United States alone, the demand for effective repair strategies is critical. This review comprehensively examines bioink development and multiscale scaffold design, critically evaluates the biomechanical and translational challenges that must be overcome, and charts a forward-looking roadmap to advance laboratory-scale prototypes into next-generation clinical implants that will redefine the standard of musculoskeletal care.

Keywords: 3D Bioprinting; Tendon/Ligament Tissue Engineering; Patient-Specific Grafts; Biomechanical Matching; Bioink Formulation

Abbreviations: dECM: Decellularised Extracellular Matrix; ACL: Anterior Cruciate Ligament; VEGF: Vascular Endothelial Growth Factor; CAD: Computer-Aided Design; GMP: Good Manufacturing Practice; ML: Machine Learning; AI: Artificial Intelligence

Introduction

The socio-economic cost burden of tendon and ligament (T/L) injuries and lesions is enormous, with millions of people being injured every year around the globe. Such injuries include both acute tears (like those of the anterior cruciate ligament (ACL) and Achilles tendon) and chronic degenerative disorders (such as rotator cuff tendinopathy). Epidemiology suggests that ACL alone results in more than 200, 000 cases each year in the United States, and rotator cuff tears involve about 30% of the over-60-year-old population, which causes chronic discomfort and functional impairment. The inherent repair capacities of T/L tissues are dreadfully low, with the main cause being their hypocellular and hypovascular nature that leads to the development of unstructured scar tissue that is less mechanically functional than the tissue used [1,2]. Existing surgical practices are mainly based on autografts, allografts, and synthetic prostheses, all of which have certain limitations. Although it offers an excellent biocompatibility, autografting is a hindrance because it is limited by the morbidity of the donor site, local pain, and a lack of a good supply of healthy tissue. For instance, autografts are limited by a donor site morbidity rate of up to 30%, while allografts and synthetic grafts exhibit failure rates as

high as 20–25% in high-demand patients. Allografts avoid problems with donor sites, but present the threat of pathogen spread and negative immune reactions. Synthetic grafts may be robust and work well in the short run, but fail in the long run with mechanical mismatch, fatigue, and the absence of biological fixation, and can readily require revision surgery.

In that sense, 3D bioprinting will be a paradigm shift, as it will become possible to create patient-specific constructs with the capability to grow to the unique geometry of an individual's defect, by utilizing medical imaging data [3,4]. In this context, the main aim of 3D bioprinting is to replicate the structure-function relationship of T/L tissues with their complex structure by laying cells, growth factors, and biomaterials layer-by-layer. Such technology enables the accurate positioning of various cell types and formation of gradient structures that closely resemble the native enthesis, which is essential to achieve positive clinical outcomes [3,5]. In this review, particular attention is paid to the nexus of bioink innovation, multiscale scaffold development, and the bio-mechanical needs of functional restoration. It does not include any forms of non-bioprinted scaffold fabrication, including electrospinning or freeze-drying, unless coupled with bioprinting to provide a targeted analysis of the multi-dimensional progress and hurdles in 3D and 4D bioprinting technologies for clinical translation [1,2].

Bioinks and Printing Strategies

The most critical phase of the successful T/L bioprinting is the development of functional bioinks, as they should meet both the printing and biocompatibility and mechanical stability requirements at the same time. Natural polymers and decellularised extracellular matrix (dECM) bioinks have become popular because of their natural bioactivity and capacity to deliver a bioimimetic microenvironment. Alginate-based strategies have received much attention due to their excellent gelation activities and capacity to sustain structure-function integrated tissue regeneration, but their absence of cell-adhesive motifs can often require further functionalization with proteins such as collagen or RGD peptides [6]. Silk fibroin has become one of the most promising substances used to manufacture patient-specific memory-shape implants because it provides a combination of high mechanical strength and adjustable rate of degradation not seen previously [7]. Recent findings have shown that fast-setting silk fibroin bioinks can be 3D printed into more intricate geometries, which retain their shape in physiological environments, and offer a framework that is strong enough to support T/L repair. Decellularised matrix-based bioink is another important advancement in the biomimetic design. Using native tendon or ligament tissue as a starting material, researchers are able to maintain the complex network of glycosaminoglycan, proteins and signalling molecules necessary to induce tenogenic differentiation by processing the native material into a printable hydrogel [8-10] (Figure 1).

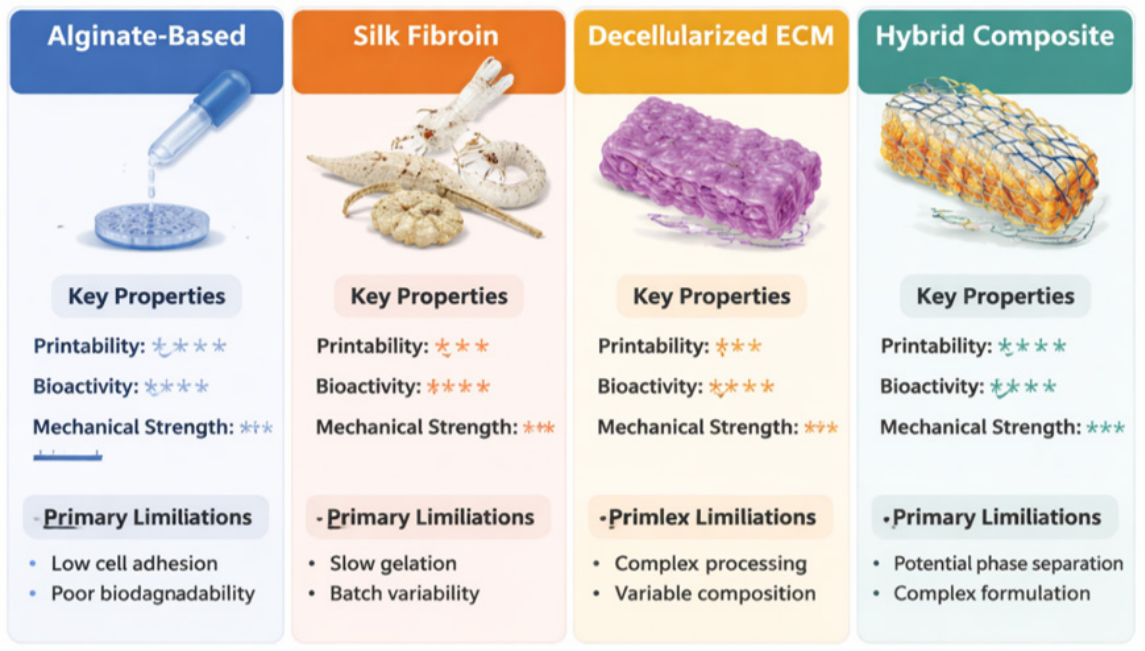

Figure 1: Comparative overview of principal bioink classes used in tendon/ligament bioprinting.

These bioinks made of dECM have demonstrated a better performance in terms of promoting cell viability and triggering the expression of tendon-specific markers than simpler natural hydrogels of pure or simple synthetic nature [11]. Nevertheless, these mechanical constraints of dECM hydrogels frequently force their application in more hybrids, wherein they are reinforced by thermoplastic polymers such as polycaprolactone (PCL) or employing chemical cross-linking mechanisms to achieve the tensile biomechanical demands of the musculoskeletal system [9,10]. More sophisticated printing techniques have developed for multi-material, multi-scale scaffolds to meet the heterogeneity of the tendon-bone interface. To create the enthesis organ, the gradient scaffolds need to be created that will switch the highly aligned, collagenous tendon zone to the mineralized fibrocartilage, and then, ultimately, to the underlying bone [4,12]. Multi-nozzle systems can be used to print a range of bioinks sequentially, or simultaneously, with spatial control of mechanical and biological properties [13]. To illustrate, rotator cuff regeneration multilayered scaffolds have been developed where the different layers used to reproduce the tendon, cartilage, and bone stages are effective in facilitating the regeneration of the tissues as a unified unit [14]. The multiscale designs are essential to minimize the stress concentrations at the interface, which is the major location of failure in the traditional repair endeavour.

They are also improved by the bioactivity of these constructs by incorporating the growth factor delivery systems and genetic functionalization. Continuous release of Platelet-Derived Growth Factor-BB (PDGF-BB) and Vascular Endothelial Growth Factor (VEGF) in the bioprinted scaffolds has been demonstrated to facilitate high healing rates through stimulating cell growth and angiogenesis [15]. Adding these factors to the bioink formulation, researchers will be able to achieve a controlled release profile that is similar to the phases of the natural healing cascade. Moreover, genetic and bioactive functionalization of bioinks can enable the encapsulated cells to produce therapeutic proteins locally, which is a long-term stimulus to promote maturation of tissue [16]. This strategy takes further than mere scaffolding to a form of producing living grafts that actively engage in the regeneration process. One of the most significant advances enabling clinical translation is the development of a fully integrated, patient-specific design pipeline that transforms individual anatomy into a precisely fabricated graft. The workflow begins with the acquisition of high-resolution medical imaging, typically MRI for soft tissue delineation or CT for bony landmarks, which captures the precise three-dimensional geometry of the injury site, including defect dimensions, surrounding tissue architecture, and joint kinematics.

These imaging datasets are then segmented and converted into Computer-Aided Design (CAD) models using specialized biomedical software, generating a digital template that faithfully reproduces the patient's unique anatomical contours [3,5]. The CAD model is subsequently translated into a layer-by-layer deposition program that directs the bioprinter with micron-scale spatial resolution, specifying the precise location, composition, and density of each bioink layer. This individualized workflow ensures that the printed graft conforms exactly to the defect space, minimising intraoperative trimming and reducing the risk of mechanical mismatch at the implant margins while simultaneously enabling zone-specific deposition of distinct bioink formulations to recreate the native tissue gradient [3,5]. Looking ahead, coupling this pipeline with real-time intraoperative imaging and 4D-responsive materials could yield grafts that are not only patient-specific in shape but also dynamically adaptive to the evolving mechanical environment of the joint post-implantation [17].

Critical Challenges

With crucial technological advancements, the mechanical property gap is the largest challenge facing bioprinted T/L grafts. The properties of native tendons and ligaments are highly anisotropic, tensile, and complex viscoelastic, with creep and stress relaxation. The majority of present bio-printed hydrogel constructs are unable to compete with the mega-Pascal tensile-modulus range necessary to support immediate post-operative loading [5]. Moreover, these grafts should be able to endure millions of loading cycles throughout their lives. Fatigue life and response to cyclic loading are not frequently considered in laboratory studies, but they are critical to clinical success [2,18]. In the absence of the means to resist these mechanical strains, the graft is prone to early tear or irreversible deformation, without which it causes clinical failure. The rebuilding of the enthesis is yet another complication. Cell types, extracellular matrix composition and mineral density provide a complex gradient of transition in the compliant tendon to the stiff bone. Mimicking this gradient is technically challenging with 3D bioprinting, and the deposition of the mineralized and non-mineralised bioinks has to be controlled very accurately [4,12]. Gradient scaffolds have demonstrated potential in vitro and in vivo, it has not yet been possible to assume seamless biological and mechanical integration in the tendon-bone interface. Inability to reproduce this interface correctly produces stress concentrations which ultimately cause graft detachment or secondary injury [13].

Vascularisation and innervation are also essential in the survival and functionality of large-scale bioprinted grafts. Tendons are an inherently hypovascular tissue: while this hypovascularity limits nutrient delivery and slows natural healing, making it one of the central challenges in tendon repair it also confers a relative advantage: the low metabolic demand of tendon tissue may simplify the bioreactor maturation process compared to highly vascularized organs such as the liver or heart, potentially reducing the oxygenation requirements during in vitro conditioning. Nevertheless, there remains a special blood supply to the surrounding sheath and to the enthesis, where there is a need to deliver nutrients and to remove metabolic wastes. The majority of existing approaches to bioprinting are aimed at the major structure of the tissue, but do not account for the complex net-

works of microvessels and nerves essential to homeostatic services and proprioception [2,19]. In case of clinical-scale constructs, the absence of an internal vascular network causes core necrosis with cells dying in the centre of the graft because of oxygen and nutrient deprivation prior to host vessels invading the scaffold [19]. Lastly, there are large regulatory, Good Manufacturing Practice (GMP), and evidence gaps that hinder the path to clinical translation. Clinical application needs to undergo vigorous testing in large animal models that replicate human biomechanics and healing response well in benchtop research. A lot of the data is at the moment restricted to small animal research, or even brief follow-ups [3].

Moreover, the regulatory environment of 3D bio-printed products, which sometimes include a combination of cells, materials and bioactive factors, is dynamic. It is necessary to ensure that protocols of bioink sterilisation, cell characterisation, and quality management are standardised to meet agency demands, such as the FDA or EMA demands [1,19]. The mass clinical use of bioprinted T/L grafts will be unachievable without a clear regulatory pathway and well-documented long-term outcomes of large-animal trials [3].

Future Perspectives

The future of T/L regeneration is the development of 3D-bioprinting to 4D-bioprinting. Different to other advancements in bioprinting technologies, 4D bioprinting involves the concept of time, whereby stimuli-responsive biomaterials are used, which can assume new shapes or characteristics based on external factors (temperature, pH, or mechanical stress, etc.) [17,20]. Such a technology would aid in the production of grafts which would respond dynamically to the mechanical environment of the joint following implantation, initially giving initial stability to the graft which would then progressively dampen to permit the natural remodelling of the tissue. Optical bioprinting methods (light-based) provide high resolution and the potential to program intricate shape changes, which can be applied to produce grafts that can be "locked-in" to bone tunnels or grow to close irregular defects [20]. Machine learning (ML) and artificial intelligence (AI) will have a significant role to play in maximizing the design of scaffolds and the bioprinting procedure. With the help of AI algorithms, it is possible to process large amounts of material properties, cell behaviour, and printing setting data to forecast the most valuable settings to use in the case of one specific patient [3]. This may save a lot of time on trial and error in the laboratory. Moreover, AI-based in vivo bioprinting, where the printing device is used on the patient during the operation, may transform the rupture treatment of complex ruptures since the printer can adapt in real-time based on intraoperative tissue appearance and mechanics.

Beyond intraoperative AI, the emerging paradigm of digital twins, patient-specific computational models calibrated with real biological data, offers a powerful framework for ML-based bioink optimization and scaffold design, enabling virtual testing of thousands of parameter combinations before a single construct is printed, thereby substantially reducing laboratory trial-and-error iterations [3]. It will be necessary to combine the use of advanced growth factor delivery and bioreactor maturation to create functional tissues. The development of advanced bioreactors, where bioprinted constructs are subjected to biomechanical loading during the maturation phase, is likely to be part of future strategies. The mechanical training is important in stimulating cell orientation and maturation of collagen fibres, which are required to attain the desired tensile properties [18]. In conjunction with the continuous administration of numerous growth factors that recapitulate the normal healing kinetics, these adult grafts will be much better prepared to meet the clinical environment requirements [15].

Conclusion

Three-dimensional bioprinting has evolved from a theoretical concept into a transformative platform for delivering patient-engineered, biomimetic tendon and ligament repair grafts. The convergence of dECM bioinks, gradient interface design, and personalized anatomical modelling represents the current state of the art; however, the field stands at a pivotal crossroad where mechanical fidelity, biological integration, and clinical scalability must be simultaneously addressed. The persistent biomechanical gap must be addressed through a prioritised research agenda focused on advanced material reinforcement and standardized bioreactor maturation protocols. Key priorities for the field include:

(i) Standardization of bioink formulations and GMP-compliant manufacturing workflows;

(ii) Integration of real-time mechanical and biochemical sensors within bioreactor systems to enable adaptive conditioning; and

(iii) Execution of well-powered, long-term large animal trials that faithfully replicate human joint biomechanics and healing biology.

Achieving these milestones will also require sustained investment in vascularisation strategies and a clear, internationally harmonized regulatory pathway for combination cell-material devices [5]. Through the convergence of 4D bioprinting, artificial intelligence, and mechanobiology, the next generation of bioprinted constructs will transcend the role of passive mechanical substitutes, emerging as truly living, responsive grafts. Ultimately, the successful translation of these technologies holds the promise of redefining the standard of care in musculoskeletal medicine, offering patients not merely a repair but a genuine biological restoration that is durable, functional, and uniquely their own [3,5].

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