New frontiers of tendon augmentation technology in tissue engineering and regenerative medicine: a concise literature review

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Abstract

Tissue banking programs fail to meet the demand for human organs and tissues for transplantation into patients with congenital defects, injuries, chronic diseases, and end-stage organ failure. Tendons and ligaments are among the most frequently ruptured and/or worn-out body tissues owing to their frequent use, especially in athletes and the elderly population. Surgical repair has remained the mainstay management approach, regardless of scarring and adhesion formation during healing, which then compromises the gliding motion of the joint and reduces the quality of life for patients. Tissue engineering and regenerative medicine approaches, such as tendon augmentation, are promising as they may provide superior outcomes by inducing host-tissue ingrowth and tendon regeneration during degradation, thereby decreasing failure rates and morbidity. However, to date, tendon tissue engineering and regeneration research has been limited and lacks the much-needed human clinical evidence to translate most laboratory augmentation approaches to therapeutics. This narrative review summarizes the current treatment options for various tendon pathologies, future of tendon augmentation, cell therapy, gene therapy, 3D/4D bioprinting, scaffolding, and cell signals.

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Introduction to tissue engineering and regenerative medicine (TERM)

In recent years, advances in biomedical research have produced significant milestones in new drug discovery, medical devices, and clinical procedures. One breakthrough of biomedical research advancements in the past three decades was the emergence of TERM. The intention of this field is based on the idea that tissue and organ reconstruction can restore patient’s normal lives after organ loss/injury. The terms tissue engineering (TE) and regenerative medicine (RM) are typically used separately and interchangeably to mean one thing (TERM), although there is a marked difference in the technicalities of the fields. TE focuses more on creating in vitro bioartificial tissues or cellular products to repair tissues within the body and involves in vivo alteration of cell growth and function through the implantation of suitable cells isolated from donor tissue and bio-compatible scaffold materials. In contrast, RM focuses on endogenous tissue formation. The three most important components of TERM are biomaterials, cells, and signals.

Although a well-defined field (TERM) has recently been developed, its foundation can be traced back to the year 300 BC in Indian writings that described skin grafting in Sanskrit texts. TERM became recognized in the mid-1950s when the first kidney transplant between identical twin brothers was successfully performed. The field aims to solve problems related to diverse backgrounds, such as acute or chronic degenerative diseases, trauma, aging, and congenital defects, and hence overlaps with other disciplines, including biomaterials, nanotechnology, stem cell biology, developmental biology, engineering, and medicine. In the field of medicine, orthopedics has greatly benefited from the technological evolution of TERM. However, to date, tendon TE and regeneration research has been limited and lacks the much-needed human clinical evidence to translate most laboratory augmentation approaches to therapeutics. Previous review articles have also performed a similar review; however, the current study conducted an extensive review of current literature to help with the limited translation of tendon augmentation in clinical practice and provide a better understanding of tendon repair in TERM.

Search strategy

A review of published articles on tendon augmentation was performed. Scientific literature was searched in relevant databases (Google Scholar, Scopus, PubMed, and Web of Science) using the terms “(regenerative medicine) AND (tissue engineering) AND (tendon repair OR tendon augmentation) AND (bio-fabrication)”. The search was conducted with publication language restricted to English. The titles of articles were reviewed, followed by the abstracts.
and full texts. After the removal of duplicates and unrelated papers, 96 articles were used in this narrative review. This article does not contain any studies with human participants or animals performed by any of the authors. Therefore, ethical approval and informed patient consent were not required.

**TE in tendon/ligament augmentation**

TE research in tendon augmentation intensified in the early 1980s, resulting in the first commercial product Gore-Tex Cruciate Ligament prosthesis (WL Gore and Associates, Newark, DE, USA) being approved by the Food and Drug Administration (FDA) on 10 October 1986. Since 1986, more commercial products have been approved, mostly in the USA by the FDA but also in Europe and across the world. Commercial augmentation products are being developed for the increased tendon injury burden from workplaces and age-related conditions, with approximately 30% to 50% of sports injuries involving tendon injuries. Currently, surgical repair remains the gold standard treatment for tendon/ligament rupture. However, the healing process is naturally lengthy relative to that of other soft tissues. This is partly because tendons are tissues of high activity with a poor blood supply, supporting fundamental locomotion of the body. As a result, they are highly prone to healing failure, thereby increasing morbidity and additional treatment costs and placing an economic burden on patients and health systems.

TERM approaches have been studied and proposed as promising alternatives to improve the quality of tendon healing. The fields of engineering, nanotechnology, molecular biology, and materials science are used alone or in combination with cells, scaffolds, and bioactive molecules in various TERM approaches. Despite showing great potential, tendon augmentation suffers from limited evidence in the literature to support the clinical use of various scaffold biomaterials. This is partly because there is a poor understanding of the basic biology of tendon development, signal transduction, mechanotransduction, and mechanisms underlying tendon pathogenesis and healing and limited translational animal models and well-designed preclinical studies, all because there are only a few researchers working in this area.

**Tendon development, histology, and physiology**

Tendons together with muscle, muscle connective tissue, ligament, bone, nerves, and blood vessels are part of the musculoskeletal system, which is vital for structural support, locomotion, and movement. The main function of tendons is to join muscles to bones and transfer forces necessary for movement. The embryological derivative of tendons is the ectoderm. Tenocytes are mature tenoblasts found in the tendon that were previously thought to be the only resident cells before the discovery of tendon stem cells (TSCs). Tenocytes and tenoblasts represent nearly 90% to 95% of the cells within the tendon, with the other 5% to 10% consisting of chondrocytes, synovial cells, and vascular cells.

Tenocytes and tenoblasts are specialized fibrocytes and fibroblasts, respectively, that secrete extracellular matrices, such as collagen, proteoglycans, and other proteins. Tenocytes control the repair, maintenance, and turnover of the extracellular matrix in response to external stimuli and stress. Tendons are mainly composed of collagen, which accounts for 70% to 80% of their dry weight, including 95% type 1 collagen and 5% type 3 collagen present in the
epitenonium and endotenonium.\textsuperscript{32} Tendons have collagen fibrils that bundle to make collagen fibers, forming fascicles, and bundles of fascicles from the fascicular matrix. Endotenon contains blood vessels, lymphatics, and nerves, and its outward continuation forms the epitenon, a synovial-like membrane that prevents adhesion of the tendon to other adjacent tissues.\textsuperscript{33}

TSCs are in some ways different from tenocytes, including differences in cell marker expression, proliferative and differentiation potential, and morphology.\textsuperscript{30} TSCs differentiate into adipocytes, chondrocytes, and osteocytes \textit{in vitro} and form tendon-, cartilage-, and bone-like tissues \textit{in vivo}.\textsuperscript{34} The study by Zhang J et al. showed that low mechanical stretching at 4\% stimulated the differentiation of TSCs into tenocytes, whereas stretching at 8\% induced the differentiation of a sub-population of TSCs into adipogenic, chondrogenic, and osteogenic lineages.\textsuperscript{34} Therefore, understanding the mechanobiology of TSCs can potentially improve the effective repair or regeneration of injured tendons.

The microstructure of tendons also comprises connective tissue tendon sheaths, fibrous sheaths, synovial sheaths, peritenon sheaths (paratenon), reflection pulleys, and tendon bursae. These structures are specialized to enhance tendon efficiency by improving the sliding motion of the tendon tissue, reducing friction with neighboring anatomical structures, and preventing the tendon from losing its course of action during muscle contraction.\textsuperscript{35}

**Tendon pathologies and current approaches to management**

A summary of the management of tendon pathologies is shown in Table 1. Tendon injuries remain a significant cause of both work-related and sport-related injuries.\textsuperscript{15} The repair of tendon injuries is a lengthy process that frequently results in a poor structural, mechanical, and functional quality of the healed tissue. At present, the clinical options for treating tendon injuries are often unsatisfactory, especially in elderly populations.\textsuperscript{35}

**Novel methods used in tendon augmentation**

**Gene therapy**

In the TE of tendons, genetic vector transfer is used as a biological delivery system to deliver the encoded gene products to the site of pathology to promote the local repair and regeneration of damaged tissues.\textsuperscript{35,67--69} Identifying and transferring genes into a local cell, resulting in the translation of the gene into specific protein-like growth factors, is the basis of this approach. Growth factors, such as vascular endothelial growth factor (VEGF), growth differentiation factor-5, platelet-derived growth factor-b (PDGF-b), and insulin-like growth factor-1 (IGF-1), are among the previously studied growth factors, and their effects have been characterized in local tendon cells.\textsuperscript{70} Localized gene transfer allows focal post-translational protein synthesis, which leads to greater biological activity and a reduced risk of activating immune reactions.\textsuperscript{35} Because of poor blood supply to joint structures, such as tendons, it is difficult to deliver therapeutics intravenously, intramuscularly, and orally without exposing the body systemically to the therapeutic agent. Therefore, local delivery methods, such as gene transfer, prove to be more advantageous.\textsuperscript{71,72} An additional benefit of using a gene-therapy, tissue-engineered approach to affect tendon healing is that it allows the physician to select specific growth factors in the tendon-healing cascade from well-documented sources.\textsuperscript{70}
Table 1. Summary of the management of tendon pathologies.

| Disease/etiology | Description | Current management | Potential management options |
|------------------|-------------|--------------------|-------------------------------|
| Ruptures/Trauma  | Partial or complete tear with pain (may be absent), loss of function, loss of strength, and feeling of emptiness on palpation | Surgical repair, rigid casting or functional bracing, functional rehabilitation | Tendon-bone insertion repair<sup>20,25</sup> Growth factors and cytokines, gene therapy, and tissue engineering with MSCs<sup>11</sup> or TDSCs and poly(LLA-CL)/Col scaffolds<sup>38</sup> | |
| Paratenonitis    | An inflammatory reaction in the outer sheath of cells that surround the tendon. Pain, tenderness, swelling, crepitation, and warmth (early term). For example: Achilles paratenonitis | Operative treatment<sup>40</sup>, conservative management (ice, night braces)<sup>39,40</sup> | Eccentric exercises, extracorporeal shockwave therapy, deproteinized hemodialysate, and topical glyceryl nitrate<sup>24,41,42</sup> | |
| Tenosynovitis    | Disease of the synovial sheath itself. Pain, tenderness, swelling of the sheath, crepitation, and warmth (early term). For example: De Quervain disease | Infectious tenosynovitis: antibiotics and/or surgical treatment<sup>43</sup> Open drainage, catheter irrigation<sup>13</sup> Non-infectious: modification, splinting, glucocorticoid injections, NSAIDS, DMARDS, surgical intervention<sup>44,45</sup> | Nanomolecular interventions have the future potential of use in enhancing the healing of tendons<sup>46</sup> | |
| Stenosing tenosynovitis | An inflammatory condition involving the synovial sheath of a tendon. Pain, crepitation, nodule on palpation, and triggering in the finger. Example: trigger finger | Conservative (corticosteroid injections<sup>48</sup>), open surgical and percutaneous release<sup>49,50</sup>, open debridement, irrigation, and primary wound closure<sup>51</sup> | Nanomolecular interventions have the future potential of use in enhancing the healing of tendons<sup>46</sup> | |
| Tendinopathy (tendinitis and tendinosis) Pathogenesis: 1) tendon cell response, 2) collagen disruption and, 3) inflammation<sup>119</sup> | Degeneration of tendon structure (wear and tear). Pain, localized tenderness, nodule on palpation. For example: lateral epicondylitis and rotator cuff tendinopathy.<sup>32</sup> | An exercise-based rehabilitation program and adjunct interventions for pain Adjuncts to exercise therapy: PRP injections, electrophysical agents, medications<sup>52-54</sup>, low-energy laser therapy, NSAIDS<sup>15</sup> | Hyaluronic acid<sup>55,56</sup> autologous tenocyte/fibroblast implantation<sup>57</sup>, other cell-based therapy<sup>25</sup> growth factors<sup>20</sup> stem cells, and botulinum toxin<sup>58</sup> have unknown effects<sup>53</sup> tendon graft augmentation<sup>20</sup> | |

(continued)
An alternative novel approach to using pure vectors is the application of gene-modified sutures, as demonstrated by Zhou et al.73 Plasmids, such as pEGFP-bFGF, are loaded onto nanoparticles to form nanoparticle/plasmid complexes, and then the complexes are attached to the surface of polydopamine-modified sutures to prepare nanoparticle/plasmid complex-coated sutures, which are then used for tendon repair to promote tendon healing. The outcome of their study showed that gene-modified sutures (nanoparticle/pEGFP-bFGF and pEGFP-VEGFA complex-coated) improved tendon healing by increasing tendon healing strengths, enhancing gliding function, and inhibiting adhesion formation without adverse effects on host tissues.73 Table 2 summarizes studies on novel methods applied in tendon management.

**Cell therapy**

Cells are among the three pillar components of TERM. Stem cells, sometimes called “medicinal stem cells,” work effectively as growth factor factories or drugstores in vivo.95 Stem cells can repopulate the injured tissue and stimulate the body’s healing properties. In tendon TE, tenocytes, TSCs, bone marrow-derived mesenchymal stem cells, MSCs, pluripotent stem cells, and embryonic stem cells are the most commonly used and most promising. The current problems faced in TE cell therapy are the identification and extraction of these cells and the identification of cell markers to easily manipulate them for a better understanding of tendon pathophysiology. A 2010 study reported that TSCs differed from tenocytes in morphology in culture, proliferative potential, stem cell marker expression, and differentiation potential.30 The application of undifferentiated stem cells for the repair of tendon injuries, such as bone marrow-derived mesenchymal stem
Table 2. Novel methods applied in tendon management.

| Method | Key properties | Comment | Citation |
|--------|----------------|---------|----------|
| **a. Tendon 3D bioprinting methods** | | | |
| Extrusion-based bioprinting | Cellular-based bioinks | Tendon 3D bioprinting has the potential to improve in vivo biocompatibility, cell cytoskeleton alignment along the long axis of the tendon graft, upregulation of tendon biomarkers in cells seeded on the graft, and mechanical properties to match those of the native counterpart. | 27, 74–76 |
| Inkjet bioprinting | Tendon scaffolds | | |
| Laser-assisted bioprinting | Human tenocytes | | |
| Stereolithography | Bioprinters, bioreactors | | |
| **b. Signals: growth factors and cytokines** | | | 11,27,77,78 |
| IGF, TGF-b1, CDMP, VEGF, PDGF, PRP, FGF, rhGDF | Signaling molecules that induce cell chemotaxis, proliferation, matrix synthesis, and differentiation in normal and pathophysiological conditions, such as growth, healing, and repair. | |
| **c. Cell therapy** | | Very promising, but current problems faced are the identification and extraction of cells and identification of cell markers of these cells to easily manipulate them. | 10,79–81 |
| Tenocytes, pluripotent stem cells, TSCs | | | |
| **d. Scaffolds** | Collagen, chitosan, PGA, PLA, PLGA, CaP, TCP, HA, silk proteoglycan, glycoprotein, fibronectin, and thrombospondin | Function as a provisional template for the interactive trafficking of cells and the creation of the extracellular matrix, offering structural support for the freshly made tissue. The scaffold should mimic the native tissue's mechanical function, topography, geometry, and porosity to recreate the native microenvironment and help the adhesion, growth, and differentiation of the populating cells. | 33,82 |
| (i) biological, (ii) synthetic and (iii) composites | | | |
| **e. Gene therapy: vector and or hybrid** | DNA genome | Nanoparticle/plasmid complexes have a high transfection efficiency. They improve tendon healing by increasing tendon healing strengths, enhancing gliding function, and inhibiting | In vitro: 73,83 |
| Nanoparticle/pEGFP-bFGF, pEGFP-VEGFA, Adenovirus, Adeno-associated | Double-stranded Nanoparticles | | In vivo: 83,84 |
| | | | |
| | | (continued) | |
Table 2. Continued.

| Method          | Key properties                                         | Comment                                                                 | Citation |
|-----------------|--------------------------------------------------------|------------------------------------------------------------------------|----------|
| o virus         |                                                        | adhesion formation without adverse effects on host tissues.            |          |
| o Retrovirus    |                                                        | Straightforward production, efficient, transduces non-dividing cells, wide host range, inflammatory, antigenic | In vivo: 85–87 |
| o Lentivirus     |                                                        | Widely used in clinical trials, with one well-publicized death         |          |
|                 | Non-integrating                                       | Transduces non-dividing cells, wild-type AAV causes no known disease, non-inflammatory, difficult to produce, small carrying capacity | In vivo: 88–91 |
|                 | Multiple serotypes                                    | Possible to engineer AAV with a double-stranded DNA genome             |          |
|                 | Double-stranded DNA genome                            | Increasingly popular for clinical trials because of safety            |          |
|                 | RNA genome                                            | Straightforward to produce amphotropic virus and has a wide host range| In vivo: 70, 92 |
| Integrating     | Transduction requires host cell division, risk of insertional mutagenesis | Usually used in ex vivo gene delivery, has been widely used in clinical trials, insertional mutagenesis has caused leukemia |          |
|                 | Wild-type AAV has a single-stranded DNA genome         |                                                          |          |
|                 | Multiple serotypes                                    |                                                        |          |
|                 | Reombinant AAV is non-integrating                     |                                                        |          |
|                 | A wild-type virus is integrating                       | Transduces non-dividing cells, very high levels of transgene expression | In vivo: 93, 94 |
|                 |                                                        | Risk of insertional mutagenesis, but non-integrating vectors developed |          |
|                 |                                                        | Increasing use in clinical trials                                    |          |

Extracellular matrix (ECM), insulin-like growth factor (IGF), ribonucleic acid (RNA), deoxyribonucleic acid (DNA), transforming growth factor-beta 1 (TGF-b1), cell-derived microparticles (CDMPs), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), platelet-rich plasma (PRP), fibroblast growth factor (FGF), recombinant human growth and differentiation factor (rhGDF), tendon stem cells (TSCs), polyglycolic acid (PGA), poly-dl-lactic-co-glycolic acid (PLGA), poly-l-lactic acid (PLLA), polyactic acid (PLA), hydroxyapatite (HA), tricalcium phosphate (TCP), calcium phosphate (CaP), adeno-associated virus (AAV), vascular endothelial growth factor-A (VEGFA), basic fibroblast growth factor (bFGF), plasmid enhanced green fluorescent protein (pEGFP).
cells (MSCs), adipose tissue-derived MSCs, embryonic stem cells, embryonic stem-like cells, adipose-derived nucleated cells, umbilical cord blood-derived MSCs, and peripheral blood-derived mesenchymal stem cells, has been well characterized. Furthermore, the author mentions that MSCs used in tendon regeneration have the potential to recruit other MSCs or progenitor cells to the injury site by producing a variety of cytokines and paracrine factors, thereby improving the regeneration potential.

Challenges with cell therapy mainly include the efficacy evaluation of MSC therapy, which is subject to the use of appropriate control groups, severity and size of the lesion, time between injury and implantation, number of stem cells for implantation, models of tendinopathy (e.g., collagenase or surgical disruption), and opting for single or multiple injections.

**Signals: growth factors and cytokines**

Growth factors are signaling molecules that induce cell chemotaxis, proliferation, matrix synthesis, and cell differentiation in normal and pathophysiological conditions, such as growth, healing, and repair. The regulation of these signals during tendon injury repair is of great importance, especially in controlling the amount of scar tissue production. Extensive scar tissue at the healing attachment site may predispose patients to impingement post-operatively. Important factors to consider when adding growth factors to cell culture media to trigger tenogenic differentiation are incubation time and cell type. In clinical scenarios, several modes for the delivery of growth factors to the injury site can be applied, including direct local injection and the use of impregnated sutures or scaffolds. Impregnated sutures or scaffolds are better at delivering growth factors to the specific area of injury without the overflow loss associated with local injection. However, local injection is comparatively non-invasive, simple, and quick, although growth factors delivered in this way only remain at the site for a short duration.

IGF, transforming growth factor β1 (TGF-β1), and cartilage-derived morphogenic protein growth factor-1, -2, and -3 are equivalent to human bone morphogenic protein (BMP)-14, -13, and -12. PDGF, epidermal growth factor, platelet-rich plasma, VEGF, interleukin-10, recombinant human osteogenic protein-1, connective tissue growth factor, fibroblast growth factor (FGF), and recombinant human growth differentiation factor have all been characterized in terms of their roles in tendon injury repair.

In several studies, PDGF-stimulated DNA and matrix synthesis in tendon cells increased the expression of cell surface integrins, which play critical roles in tendon repair. IGF-1 also enhances healing by increasing DNA, collagen, and glycosaminoglycan production. In vitro and in vivo studies have elucidated the ability of IGF-1 to decrease swelling and simultaneously increase cell proliferation, collagen synthesis, and DNA content. FGF2 is among the most promising cell signals in tendon augmentation and has been widely reported to increase tendon/ligament revascularization, cell proliferation, and collagen production and stimulate new bone formation, accelerating tendon-to-bone healing.

**Scaffolding**

According to Mota et al., a scaffold is a material that functions as a provisional template for the interactive trafficking of cells and the creation of the extracellular matrix, offering structural support for the freshly made tissue. Tendon scaffolding material comes in three main forms: biological, synthetic, and composite.
| Type of scaffolding | Source | Strengths | Weaknesses | Examples | Citation |
|---------------------|--------|-----------|------------|----------|----------|
| Biological          | Mammalian tissues, such as human, porcine, bovine, and equine | High hydrophilic properties, Low immunological response, Cell adhesive | Low mechanical properties, Degradation-related products can be cytotoxic, and the materials are mechanically weaker than healthy musculoskeletal tissue | Collagen type I composite, Chitosan | 14,16,33 |
| Synthetic           | Chemical agents | High mechanical properties, Versatility, Large-scale manufacturing, limited disease transmission, controlled degradation | Low hydrophilic properties, High immunological response, Selective cell adhesion | Carbon, Dacron, silicone, nylon, polyester, PGA, PLA, PEO, PLLA | 14,16,33,96 |
| Composite           | The mixture of biologicals and or synthetics, Polymer-ceramic composite materials | Can be tailored to match different mechanical properties of native tissue, Improves biocompatibility and cell adhesive potential and decreases the degradation rate of scaffolds | Low degradability and poor mechanical strength | Chitosan/alginate, Chitosan/hyaluronic acid, Bovine type 1, collagen, and chondroitin-6-sulfate | 14,16,33 |

Poly-l-lactic acid (PLLA), polyethylene oxide (PEO), polyglycolic acid (PGA), polylactic acid (PLA).
compares the types, sources, strengths, and weaknesses of scaffolding material used in tendon augmentation.

Regardless of the type, an effective scaffold should have appropriate biocompatibility, biodegradability, biokinetics, porosity, and biomechanical properties close to the target natural tissue’s predefined geometry and size. From Table 3, it is clear that all three forms of scaffolds have strengths and weaknesses. Synthetics have a great deal of versatility and high mechanical strength and hold a greater potential for high-volume industrial production than others. However, synthetic scaffolds are relatively immunogenic, have low hydrophilic properties, and lack sufficient cell adhesive properties. Biologic scaffolds are harvested from mammalian tissues, such as human, porcine, bovine, and equine, and are the most studied type of scaffolding. Biologics have adequate cell adhesion properties, low immunogenicity, and high hydrophilicity, although their mechanical strength is the lowest. Composite scaffolding attempts to combine the advantages of biological and synthetic scaffolds, offering improved biocompatibility and lower degradability; however, its mechanical properties still present a challenge.

The ideal augmenting scaffold would be able to stimulate endogenous tendon tissue regeneration during degradation and reduce in vivo mechanical forces on tendon repair during post-operative healing. Biologics (extracellular matrices) have great potential in achieving this; however, current clinical evidence is limited because there are only a few well-conducted human studies in this area. Table 4 describes the in vivo and in vitro laboratory studies on scaffolding materials in tendon augmentation.

Nanotechnology in tendon augmentation

The National Science Foundation defines nanotechnology as “the ability to understand, control, and manipulate matter at the level of individual atoms and molecules, as well as at the “supramolecular” level involving clusters of molecules (in the range of about 0.1 to 100 nm) to create materials, devices, and systems with fundamentally new properties and functions because of their small structure.” In nanomedicine, new advancements in nanoadjuvants, NanoKnife, oncology, orthopedic drug delivery, implantable materials, vertebral disk regeneration, and diagnostic modalities have been described and currently hold a promising future in TERM.

The use of nanomedicine in tendon regeneration and repair is related to the individual physicochemical properties of particles and holds promise for improving extrinsic and intrinsic tendon healing with less adhesion compared with postsurgical adhesion. Nanofibers, such as Poly (caprolactone)-Based Nanofiber Electrospun Scaffolds, have shown promising results in various tissue regeneration applications in bone, cartilage, skin, tendon, ligament, and nerve. Silver nanoparticles (AgNPs) are among the most widely used nanoparticles because they have anti-microbial and anti-adhesion effects, modulate the extracellular matrix composition, and promote the proliferation of primary tenocytes to AgNPs and the production of extracellular matrix components. An earlier study reported that a polylactic-co-glycolic acid nanofiber-based scaffold system showed potential for functional human rotator cuff repair. Nanoparticles can also be used as combination therapies. For example, Zhou et al. delivered a gene therapy to modulate gene expression, enhancing tendon healing and decreasing adhesions. The researchers transfected disrupted digital flexor tendon tenocytes with miRNA plasmids complexed with polylactic-co-glycolic acid [nanoparticles to form nanoparticle/TGF-β1 miRNA plasmid (nanoparticle/plasmid)],
Table 4. *In vivo* and *in vitro* laboratory studies on scaffolding materials in tendon augmentation.

| Composite/hybrid | Model | Result/scaffold properties | Cell/tissue integration | Citation |
|------------------|-------|-----------------------------|-------------------------|----------|
| PLGA nanofiber-based scaffold | *In vitro*: Human rotator cuff cells | Rotator cuff fibroblasts cultured on the aligned scaffolds attached along the nanofiber long axis, whereas the cells on the unaligned scaffold were polygonal and randomly oriented. | Observations demonstrate the potential of the PLGA nanofiber-based scaffold system for functional rotator cuff repair. Moreover, nanofiber organization has a profound effect on cellular response and matrix properties and is a critical parameter for scaffold design. | 103 |
| PLGA loaded with BMSCs | *In vivo*: rabbit | These results suggest that the PLGA biodegradable scaffold loaded with allogeneic BMSCs has the potential to regenerate and repair gap defects of the Achilles tendon and effectively restore its structure and function. | All wounds healed well without any apparent inflammatory reaction or apparent lymphocyte infiltration. | 99 |
| Fiber-aligned nanofibrous scaffolds, PCL fiber-aligned mesh | *In vivo*: rats | Implanted scaffolds remained in situ without gross migration from the supraspinatus tendon during the study interval. | Scaffold attachment to the bone appeared to not be maintained. The PCL scaffolds also showed appreciable cellular infiltration and colonization at 4 and 8 weeks after injury and repair. (i) All groups demonstrated closure of the tendon-bone gap with a fibrocartilaginous interface. (ii) Dermal collagen specimens exhibited a disorganized structure with significantly more abnormal collagen fiber arrangement and cellularity than in the DBM-based repairs. | 104 |
| DBM/dermal matrix scaffold | *In vivo*: rats | The application of DBM in a rat model of chronic rotator cuff degeneration did not improve the composition of the healing enthesis compared with non-augmented controls and a commercially available scaffold. | (i) All groups demonstrated closure of the tendon-bone gap with a fibrocartilaginous interface. (ii) Dermal collagen specimens exhibited a disorganized structure with significantly more abnormal collagen fiber arrangement and cellularity than in the DBM-based repairs. | 105 |

(continued)
| Composite/hybrid | Model                      | Result/scaffold properties                                      | Cell/tissue integration                                                                 | Citation |
|------------------|----------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------|----------|
| PGA/PLA composite| In vitro: ADSCs, In vivo: rabbit | After implantation in the Achilles tendon                       | (i) Grossly, the implanted cell-seeded scaffold was integrated with the native tissue interference, with a smooth surface cord-like shape and less noticeable remaining material after 45 weeks. (ii) Tissue adhesions, described grossly to be less compared with the control. (iii) Parallel and more mature collagen fibers and longitudinally aligned cells present than in the control. | 16       |
|                  |                            | Tensile strength: 4.88 ± 8.07 MPa                               | No report of other mechanical properties.                                                |          |
| P (LLA-CL)/collagen I | In vitro: tenocytes      | Young's modulus                                                  | (i) Significantly higher cell proliferation in the nanoyarn scaffold compared with that in other scaffolds and the control. (ii) SEM showed spindle-shaped cells in both nanoyarn and aligned nanofiber scaffolds, while polygonal and random pattern cells were found in the randomly oriented fibers. (iii) Expression of tendon-specific ECM (type I collagen, type III collagen, decorin, tenascin-C, and biglycan) was significantly higher at 14 days in the nanoyarn group. | 16       |
|                  |                            | Unseeded ~2.2 MPa                                               |                                                                                         |          |
|                  |                            | Cell seeded ~3 MPa                                               |                                                                                         |          |
|                  |                            | Tensile strength                                                |                                                                                         |          |
|                  |                            | Unseeded ~3 MPa                                                 |                                                                                         |          |
|                  |                            | Cell seeded ~4.5 MPa                                            |                                                                                         |          |
| P (LLA-CL)/collagen I nanoyarn | In vitro: TDSCs, In vivo: mouse | Mechanical stress:                                                | TDSCs were used in scaffold seeding with both dynamic and static culture conditions. | 16       |
|                  |                            | The dynamic group was                                           |                                                                                         |          |

(continued)
| Composite/hybrid | Model | Result/scaffold properties | Cell/tissue integration                                                                 | Citation |
|-----------------|-------|-----------------------------|----------------------------------------------------------------------------------------|----------|
| PLA/collagen-I electrospun bundles | In vitro: tenocytes | Composite scaffolds were made from blends containing PLA/Col-I-75/25 (w/w). | (i) Tenocytes seeded on PLA/Col-I-50/50 blends exhibited a better cell adhesion |

Table 4. Continued.

Youth modulus:
The static group was 43.18 ± 6.58 MPa
The control group was 32.43 ± 5.27% MPa
Young's modulus:
The dynamic group was 51.99 ± 7.16 MPa
The static group was 34.76 ± 4.75 MPa.
The control group was 23.30 ± 3.83 MPa.

In vitro:
(i) TDSCs showed elongated fibroblast-like morphology with a significant increase in cell counts in the dynamic group at 14 days.
(ii) More cell infiltration and dense matrix in the dynamic group.
(iii) PCR confirmed increased tendon-related mRNA expression in the dynamic group.
(iv) Western blotting showed a significant increase in the protein expression levels of collagens I and III and tenascin-C in the dynamic group.

In vivo:
(i) Significantly lower number of cells at 12 weeks, with greater matrix deposition and longitudinal spindle-shaped cells in the dynamic group compared with that in other groups.
(ii) Collagen content was highest in the dynamic group, reaching 77.76% ± 6.82% of that in normal rabbit patellar tendon (174.31 ± 13.89 μg/mg).
(iii) Collagen I expression was significantly higher in the dynamic group.
| Composite/hybrid | Model | Result/scaffold properties | Cell/tissue integration | Citation |
|-----------------|-------|-----------------------------|-------------------------|----------|
| PLA/GNP and PLA/ carboxyl-functionalized carbon nanotubes (CNT-COOH) | In vitro: fibroblasts | Young's modulus PLA control: 3.99 ± 0.42 GPa PLA/CNT-COOH: 4.86 ± 0.47 GPa PLA/GNP: 4.92 ± 0.15 GPa Tensile strength PLA control: 59.90 ± 4.93 MPa PLA/CNT-COOH: 72.22 ± 1.52 MPa PLA/GNP: 58.56 ± 3.99 MPa | (i) Both produced scaffolds supported fibroblast metabolic activity and proliferation until the final assessment point (72 hours). (ii) In vivo assessment showed a lack of any local or systemic inflammatory response using NAG and NO serum levels. (iii) No associated hepatotoxicity in the histologic assessment. (iv) Histologic assessment of explanted scaffold showed the formation of a thin capsule around the implant with homogenous granulation tissue. | 16 |
| PCL/collagen-PLLA/collagen | In vitro: myoblasts, fibroblasts | Tensile strength was 0.5058 ± 0.2130 MPa The maximum strain was 18.49% ± 8.210 Young's modulus was 7.339 ± 2.131 MPa | (i) Statistically higher viability of both myoblasts and fibroblasts in all regions of the scaffold. (ii) Scaffold could support the formation of myotubes, which is essential for normal muscle-tendon junction formation. | 16 |
| Aligned PLLA nanofiber/layered ch- | In vitro: tenocytes | Maximum force to break For uncoated 2- and 3-layer scaffolds: 7.89 ± 1.5 N and | (i) Alginate coating was associated with significantly less attached proteins than the control. | 16 |
| Composite/hybrid | Model | Result/scaffold properties | Cell/tissue integration | Citation |
|------------------|-------|-----------------------------|-------------------------|----------|
| itosan-collagen hydromgel/alginate outer coating | | 7.45 ± 0.3 N | (ii) Both coated and uncoated scaffolds maintained 50% of their substance after incubation with PBS containing $10^4$ units/mL lysozyme solution. | | |
| | | For gel-coated 2- and 3-layer scaffolds: 4.76 ± 0.23 N and 6.49 ± 0.09 N. | (iii) Alamar blue and DNA concentration assessment showed high cellular viability, metabolic activity, and proliferation up to 7 days after seeding. | | |
| | | No report of other mechanical properties. | (iv) Seeded scaffolds were shown to support cellular alignment. | | |

Carboxyl-functionalized carbon nanotubes (CNT-COOH), N-acetylgalactosaminidase (NAG), nitric oxide (NO), poly-l-lactic acid (PLLA), polyglycolic acid (PGA), polyactic acid (PLA), graphene nanoplatelets (GNP), poly(lactide-co-glycolide) (PLGA), bone marrow stromal cells (bMSCs), demineralized bone matrix (DBM), poly(l-lactide-co-caprolactone) (PCL), l-lactic acid-co-ε-caprolactone (poly(LLA-CL)), deoxyribonucleic acid (DNA), tendon-derived stem cells (TDSCs), adipose-derived stem cells (ADSCs), polymerase chain reaction (PCR), phosphate-buffered saline (PBS), scanning electron microscopy (SEM).
with improved efficiency.\textsuperscript{84} Thus, nanotechnology remains a pivotal partner of tendon augmentation technology.

\textbf{3D and 4D printing/additive manufacturing (AM) in tendon/ligament augmentation}

AM, loosely called 3D printing, is a computer-assisted fabricating technique that uses precise geometry and computer-aided design to produce structures with complex geometries in a wide variety of fields. This involves the controlled deposition of a binder material laid on a powder layer using various AM techniques, such as inkjet printing and laser sintering, to produce constructs of complex geometry.\textsuperscript{82,113,114} Bioprinting is a method of AM that combines and assembles biomaterials, bioactive molecules, and cells to generate complex tissue-engineered structures.\textsuperscript{113} This technique has been widely used in TERM studies, and its application holds tremendous hope in designing and bio-fabricating organs of complex shapes and microstructures with a high degree of automation, low production cost, high speed and volume, good accuracy, and reproducibility.\textsuperscript{82,115} Bioprinting has been applied in the manufacturing of various organs and tissues \textit{in vitro}, including vascular tissues, skin, liver, neural tissue, heart, kidney, cartilage, bone, and skeletal muscles.\textsuperscript{116–118}

Although there are extremely few studies on tendon 3D bioprinting, Merceron et al. managed to bioprint a 3D complex musculotendon unit structure using 3D integrated organ printing technology \textit{in vitro}.\textsuperscript{75} In another rabbit model, 3D desktop printers were used to print an anterior cruciate ligament surgical implant. After 4 and 12 weeks, an \textit{in vivo} assessment of rabbit anterior cruciate ligament models showed that the scaffold was full of MSCs and displayed significant bone ingrowth and bone-graft interface formation within the bone tunnel.\textsuperscript{119} Moreover, in an \textit{in vivo} porcine study, Zhang et al. investigated mechanical and biological properties, fabrication methods for ligament-bone composite scaffolds, and problems between 3D printed ligament grafts and host bones in ligament reconstruction surgery using ligament-bone composite scaffolds. The team concluded that ligament-bone composite scaffolds established using the 3D printing technique accelerated the regeneration of the biomimetic ligament-bone interface.\textsuperscript{120} 3D bioprinting technology can be classified into three sub-types: inkjet-based, laser-assisted, and microextrusion-based printing.\textsuperscript{76}

Extrusion-based bioprinting (also called direct ink writing) is the most commonly used type of 3D printing in TE applications and is implemented by most commercially available systems, with several distinct advantages.\textsuperscript{76,121} Some advantages of this technique include high versatility, affordability, ease of use, multiple print heads allowing for printing multiple materials within a single construct, printability of highly viscous bioinks ($30–6 \times 10^7 \text{mPa s}^{-1}$), and printability of structures with high cell densities (including cell spheroids).\textsuperscript{27,121,122} The most significant drawback of extrusion-based bioprinting is that cell viability and functions are reduced as cells are exposed to shear stress when passing through the nozzle and pressure while in the syringe before extrusion.\textsuperscript{123} In addition, this method has a relatively lower printing speed and resolution, which is highly dependent on setup. Extrusion-based bioprinting has three sub-systems (pneumatic, piston, and screw driven), which makes it versatile and compatible with some hydrogels, including alginate, gelatin, chitosan, hyaluronic acid, Pluronic F-127, and polyethylene glycol.\textsuperscript{124,125}

Inkjet and laser-assisted techniques have tremendous resolutions and cell viabilities.
Inkjet bioprinting is fast and cheap and has diverse applicability for different types of materials. Disadvantages of the inkjet technique include limitations to bioinks with a viscosity of 3.5 to 12 mPa s \(^{-1}\) and low cell density (\(<10^6\) cells mL\(^{-1}\)). Laser-assisted bioprinting is a complex and expensive system with a high degree of precision and resolution that can print a high cell density (\(~10^8\) cells mL\(^{-1}\)). However, it is a fast-printing system with high applicability in the micropatterning of cells and biomolecules because of its high printing resolution.\(^{126}\)

Stereolithography (including digital light processing) is a complex system with high applicability in multi-material bioprinting, resolution of bioprinting (\(~1\) µm), and cell viability (>85%). It is equivalent to extrusion bioprinting in these areas but requires a large number of cells as the entire bath volume must be filled.\(^{121}\) Stereolithography has high printing costs and is restricted to only photo-cross-linkable materials, a single bioink per construct, and a uniformity (both density and distribution of phenotype) of included cells.\(^{27,121,125}\)

**Process of 3D tendon bioprinting.** The process of bioprinting (Figure 1) begins with data acquisition, during which 3D models are acquired indirectly using X-ray, computed tomography, and magnetic resonance imaging techniques to scan and reconstruct or directly using computer-aided design software. Then, bioinks are carefully selected to guarantee biocompatibility, printability, and mechanical properties. The appropriate configuration of printing parameters needs to be confirmed before bioprinting. Finally, after printing, the implanted cells should create bonds and generate some structures and functions of the natural tissue/organ through physical and chemical stimulation of the target (receptors/signals).\(^{125}\)

If 3D bioprinting can create cadaveric tendons, then it is reasonable to think that 4D bioprinting will create “living” tendons owing to automation. While 3D printing still offers more futuristic approaches, its fundamental principle faces the limitation of producing only static, non-animating constructs that lack time-dependent dimensions and ultimately fail to mimic dynamic human tissues.\(^{127,128}\) In contrast, 4D bioprinting uses smart materials that exhibit changes in physical or chemical properties in a controlled and functional manner upon exposure to an external stimulus, such as

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**Figure 1.** Illustrating the stages involved in the process of tendon bioprinting.
heat, moisture, light, magnetic field, or pH. Moreover, unlike 3D, 4D printed constructs have the five following unique properties:129,130

(i) Shape memory: material changes into a predefined shape in response to an external stimulus
(ii) Self-assembly: exposure to external stimulus induces the folding of chains and assembly into a preprogrammed shape
(iii) Self-actuating: automated actuation of material upon exposure to an external stimulus
(iv) Self-sensing: material detects and quantifies the exerted external stimuli
(v) Self-healing: damage caused in the structure is repaired without any external intervention

4D printing in orthopedics is still rare. In 2018, Haleem et al.131 postulated the potential application of 4D printing in constructing smart orthopedic 3D implants, smart multi-material printing of organs, and tissue printing. Undoubtedly, 4D bioprinting technology will lead to the development of the orthopedic specialty “smart orthopedics,” which will revolutionize the management of spinal deformities, fracture fixation, joint injuries, cartilage constructs, knee replacements, and other related orthopedic applications.132,133 Unfortunately, we did not find in vitro, in vivo, or clinical research on 4D bioprinted constructs for tendon augmentation.

Challenges faced in translational tendon research and possible solutions. The first challenge of tendon TE is the lack of adequate translational research that enhances multidisciplinary collaboration among laboratory and clinical researchers and integrates the innovative desires of the general public (patients) to form high-quality medical practices.134 Figure 2 describes the process of translational medicine in tendon research.

Translational research can be divided into five levels (T0–T4), where T0 resembles the conceptual and basic research stage, T1 shapes and provides improved ideas from basic research through early investigations in humans, and T2 encompasses the creation of effective human and clinical guidelines.134 Finally, T3 involves translating the research to practice, while T4 emphasizes outcomes and effectiveness analysis in populations.135,136

The challenges in the production of commercial products in TERM are stage related. First, the broad diversity of TERM as a research field presents an administrative challenge at translational stage T0 as some projects may require skills from various disciplines. This fundamental barrier feeds secondarily into problems encountered in laboratory studies, such as a lack of proper manipulation and appropriate acquisition of research material (cells, cell source, scaffold materials, nanoparticles, vectors, and bioreactors).137 In vitro/in vivo studies (T0–T2) on cell therapy may indicate challenges in the lack of specific and reliable markers that can label tendon-derived stem cells (TDSCs) in vitro and tendon stem cells in situ, posing a problem in cell source identification, cell isolation procedures, and cell culture marker expression. This makes it difficult to fully understand the functions of TDSCs.138,139 The lack of sufficient human subjects willing to volunteer in clinical trials affects T1 to T3.

Although 3D bioprinted tendons are promising (T0–T1), considerable work is still expected both in vivo and in vitro. The technology faces challenges in bioprinting resolution, bioprinting speed (especially for vascular structures), and scaling up to large-scale cell-based therapies because of limited oxygen and nutrient supply to the innermost parts of the bioprinted structures.
and efficient waste product elimination. However, Ramos and Moroni believe that perfusable branched systems with smaller microvessels can help bypass this bottleneck.113

Currently, 4D bioprinting is largely conceptual (T0) in general, and it is not yet widely applied in orthopedics. There are very few laboratory studies and clinical studies on 4D printing smart orthopedics worldwide. More orthopedic research is needed in this area at all levels. The number of in vitro/in vivo studies (T0–T4) on tendon augmentation is generally limited, and there are even fewer clinical trials, indicating the slow translation of research knowledge to therapeutic products and making the evaluation of available therapeutics difficult.22,137 This situation is both caused by and results in ineffective therapeutics, mainly because the fundamental mechanisms that underlie the pathogenesis of tendon injuries and impaired healing are not well understood.21 More research funding and interdisciplinary scientific collaborations are key in TERM research T0 to T4 translation.

**Commercially available scaffolds products.** Commercial products are the final output of tendon TERM research (T0–T4). The ultimate product quality determines market demand14 and directly affects the research translation cycle (T0–T4) efficiency. Numerous biological and synthetic scaffolds have been developed and approved by various regulatory bodies globally, and a few studies have investigated their properties.14,140 In general, the mechanical and biocompatibility properties of commercially

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**Figure 2.** Process of translational research in tendon augmentation. T0 to T2 are the translational stages from basic science to human studies. T2 to T4 represent the translation of new data into clinic and health decision making.
| Product                  | Company                                      | Source                        | Regulatory approval | Citation |
|-------------------------|----------------------------------------------|-------------------------------|---------------------|----------|
| Allopatch HD            | MTF                                          | Human dermis                  | FDA                 | 141      |
| ArthroFlex              | Arthrex                                      | Human dermis                  | FDA                 | 141      |
| BioArthro               | BioArthro                                    | Human amniotic membrane      | FDA                 | 141      |
| Connect                 | Torion                                       | Porcine dermis                | FDA                 | 141      |
| Dermaplast              | BioArthro                                    | Human dermis                  | FDA                 | 141      |
| Artelon® and Sportsmesh™| Artimplant AB, Sweden and Biomet Sports Medicine (IN, USA) | Polyurethane urea polymer | FDA; Artimplant AB, Sweden | 20 |
| Bio-Blanket             | Kensey Nash Corporation (PA, USA)            | Bovine dermis                 | FDA                 | 20       |
| CuffPatch               | Arthrexal (IN, USA)                          | Porcine SIS                   | FDA                 | 20       |
| Gore-Tex® patch WL     | Gore and Associates, Flagstaff (AZ, USA)      | Gore-Tex® ePTFE               | FDA                 | 20       |
| Graftjacket®            | Wright Medical (TN, USA)                     | Human cadaver dermis          | FDA                 | 20       |
| Leeds-Keio® or Poly-tape® | Xiros plc, Neoglycins (Leeds, UK);           | Terephthalic polyethylene polyester | FDA, Europe         | 20 |
| OrthAIRADAPT®           | Permacol®                                    | Polyethylene terephthalate    | FDA                 | 20       |
| PeriPatch®              | OrthoPac®                                    | Polyethylene terephthalate    | FDA                 | 20       |
| Shelhigh No-React®      | DePuy Orthopedics (IN, USA)                  | Bovine or porcine pericardium | FDA                 | 20       |
| TissueMend              | Stryker Orthopedics (Mj, USA)                | Fetal bovine dermis           | FDA                 | 20       |

Food and Drug Administration (FDA), small intestinal submucosa (SIS), expanded polytetrafluoroethylene (ePTFE).
available products require improvements and new approaches, as discussed in the paper. Table 5 shows a list of the most widely used biologics that are commercially available for tendon scaffolds. Table 6 shows a list of the most widely used non-biologics that are commercially available for tendon scaffolds.

**Recommendations and future studies.** The future of tendon augmentation in TE lies in the strong integration of various disciplines to translate ideas into research, followed by actual therapeutics. Although research is still limited in tendon augmentation, considerable work has been conducted on stem cell biology and functional scaffold materials. These two fields require more clinical trials to improve the available knowledge of current materials. The fields of nanotechnology and 3D/4D bioprinting are key to the future development of TE and tendons in particular, and require more attention.

Future researchers should focus more on combined approaches among cell therapy, growth factors, gene therapy, nanotechnology, and AM. A good example is Zhou et al., who used gene-modified sutures loaded with nanoparticles to form nanoparticle/plasmid complexes to promote tendon healing. The outcomes reported by Zhou et al. were superior tendon healing strengths, enhanced gliding function, and inhibited adhesion formation without adverse effects on host tissues. In our review, we found limited research on 3D/4D bioprinting in orthopedics and very few studies on tendon augmentation. Therefore, the authors recommend that future studies should focus on applying 3D/4D bioprinting technologies in orthopedics, especially tendon augmentation, as they hold tremendous potential.

| Table 6. List of most widely used non-biologics commercially available for tendon scaffolds. |
|---|---|---|---|---|
| **Product** | **Company** | **Source** | **Regulatory approval** | **Citation** |
| Gore-Tex® TM | WL Gore and Associates, USA | Polytetrafluoroethylene (PTFE) | FDA, Canada, Europe | 14 |
| Lars ligament | Ligament Augmentation and Reconstruction System, Dijon, France | Polyethylene terephthalate (PET) | FDA, Canada, Europe | 14 |
| | JK Orthomedic Ltd, Quebec, Canada | Polyethylene terephthalate (PET) | FDA, Canada, Europe | 14 |
| | Yufu Itonaga Co. Ltd, Tokyo, Japan | Polyester ethylene terephthalate | FDA, Canada, Europe | 14 |
| | Xiros plc, Neoligaments, Leeds, UK | Polyester ethylene terephthalate | FDA, Canada, Europe | 14 |
| | Synthesome, Germany | Polyethylene terephthalate | FDA, Canada, Europe | 14 |
| | Torisier, France | Polyethylene terephthalate | FDA, Canada, Europe | 14 |
| | Biofiber, France | Polyethylene terephthalate | FDA, Canada, Europe | 14 |
| | Biomet Sports Medicine, IN, USA | Polyethylene terephthalate | FDA, Canada, Europe | 14 |
| | Artelon® and Sportmesh, Sweden | Polyethylene terephthalate | FDA, Canada, Europe | 14 |
| | Biofiber-CM, IN, USA | Polyethylene terephthalate | FDA, Canada, Europe | 14 |
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| | Biofiber-CM, IN, USA | Polyethylene terephthalate | FDA, Canada, Europe | 14 |
Conclusion

We are presented with an increasing global prevalence of tendon pathologies, especially among manual laborers, the sporting community, and the elderly. However, considerable improvements in techniques of tendon repair in the past decades have not led to clinically significant progress, partly because tendons are poorly perfused, heal slowly, and frequently form scar tissue. These and other factors have led to a high failure rate of treatments, joint stiffness, morbidity, and cost burden for patients. The current tendon TE scaffolds (synthetic, biologic, or composites) on the market are static and non-animating, lacking the time-dependent dimensions and failing to mimic the dynamic tissue environment and biomechanical forces required to promote optimal tenogenic differentiation for endogenous repair and regeneration. In the future, new strategies, such as 3D/4D bioprinting, may provide a rapid and promising solution for the production of smart tendon/ligament scaffolds with self in vivo regulation in response to stimuli, animating ability, and self-healing. This would lead to the development of smart orthopedics. This narrative review reported some successful laboratory studies on cell therapy, scaffolds, 3D/4D bioprinting, gene therapy, cell signals, or their combination. To successfully develop more tendon augmentation therapies via TERM approaches, further research and clinical trial investigations are needed.

Author contributions

RM conceptualized and planned the article and contributed to the writing of the manuscript. MHN, MMT, and LOZ contributed, reviewed, and edited the manuscript. JDW contributed, reviewed, and revised the final work. All the authors read and approved the final version.

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