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Review article

Natural, synthetic and commercially-available biopolymers used to regenerate tendons and ligaments

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ABSTRACT

Tendon and ligament (TL) injuries affect millions of people annually. Biopolymers play a significant role in TL tissue repair, whether the treatment relies on tissue engineering strategies or using artificial tendon grafts. The biopolymer governs the mechanical properties, biocompatibility, degradation, and fabrication method of the TL scaffold. Many natural, synthetic and hybrid biopolymers have been studied in TL regeneration, often combined with therapeutic agents and minerals to engineer novel scaffold systems. However, most of the advanced biopolymers have not advanced to clinical use yet. Here, we aim to review recent biopolymers and discuss their features for TL tissue engineering. After introducing the properties of the native tissue, we discuss different types of natural, synthetic and hybrid biopolymers used in TL tissue engineering. Then, we review biopolymers used in commercial absorbable and non-absorbable TL grafts. Finally, we explain the challenges and future directions for the development of novel biopolymers in TL regenerative treatment.

1. Introduction

Tendon and ligament (TL) undergo some of the highest mechanical loads in daily activities and sports in the body. Over-exceeded loads can result in different levels of injury overtime, such as tears or even rupture [1]. These injuries are difficult to control, usually causing long-term discomfort, and pain [2,3], and as TL have relatively low regenerative capacity, damaged tissue rarely achieves original functionality and mobility once healed.

Repaired of injured TL typically involves a biocompatible polymer, either via surgical reparative techniques using artificial TLs or tissue engineering strategies, with reconstruction using a commercially-available artificial TL being the most common clinical treatment. These artificial TLs are mainly based on non-absorbable synthetic polymers, like polyethylene terephthalate (PET) and polypropylene (PP), resulting in a permanent implantation at the injury site. Current artificial TLs cannot truly recapitulate the complexity of native TL connections, particularly in bone-tendon/ligament junction. In addition, regardless of the mechanical functionality, complications such as foreign body reactions, inflammation, or even synovitis, persist [4,5].

To overcome these challenges, there has been intense interest in the biomimicry of the native TL and their interfacial tissues through tissue engineering and regenerative medicine [6]. Different biodegradable synthetic or natural polymers have been used in the design and fabrication of TL scaffolds, considering cell integration, controlled release of therapeutic agents, mechanical stimulations, and compositional

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properties of the native TL. While natural biopolymers are popular due to their high biocompatibility and extracellular matrix (ECM) mimicking capability, biodegradable synthetic biopolymers offer excellent mechanical properties and controlled degradation rates [7]. In the last decade, many composites based on natural and synthetic biopolymers have been developed to achieve the optimal balance between biocompatibility, degradation rate, and mechanical properties. Different biofabrication techniques, like electrospinning, have been also employed to make biomimicking scaffolds for TL interfacial tissue engineering [8,9]. Since enthesis and the myotendinous junctions possess complex properties, novel biopolymers, hierarchical architectures, and signaling strategies have been combined to achieve biofunctional scaffolds [10,11]. However, it is still challenging to select appropriate biopolymers to develop complex biofunctional scaffold systems that meet the criteria for growth factor release, cellular response, biomechanical properties and control of architecture.

In-depth knowledge of biopolymers is essential in formulating novel biomaterials, choosing biofabrication method to develop the scaffolds as well as designing tissue engineering strategies (e.g. type of cell culture, growth factor and mechanical stimulations). Although several articles have recently reviewed biofabrication techniques and TL tissue engineering strategies [6,8], there are few papers discussing the role of biopolymers in TL tissue engineering and clinical treatments via commercial TL grafts. Here, we critically discuss the advantages and disadvantage of synthetic, natural, hybrid biopolymers for the fabrication of scaffolds in TL tissue engineering and commercial grafts in clinical treatments.

2. Tendon and ligament tissues

2.1. Structures and biocompositions

Tendons connect muscle to bone and transmit the force generated from the muscle to the bone to actuate movement. Hence, the generated forces in the muscles are suddenly transferred without the loss of energy due to stretching [12]. Ligaments have a similar structure to tendons, but a different function; ligaments link bones to together. Tendons and ligaments are composed of fibres formed in a hierarchical structure, as displayed in dashed blue box in Fig. 1. The smallest building block of the structure begins with collagen molecules based on three sequenced peptide chains with a diameter of approximately 1.5 nm. The group of five collagen molecules are cumulated into microfibrils, and subsequently give rise to fibrils, which correspond to the crimp pattern of TL structure [13–16]. Collagen fibrils accumulate to make up collagen fibres, with the fibres packed together again to form a fascicle bundle, which is the largest subunit of a tendon with diameters ranges from 150 to 500 μm.

From a biochemical perspective, TL are mostly composed of water (60–70%); however, collagen (27–33%) is the principal dry constituent of TL weight, with collagen type I and III (with a 9:1 ratio) being the two dominant types. One of the largest differences between tendons and ligaments is their pyridinoline content, a crosslinking compound of collagen fibres; tendons may have up to 34% higher content of the crosslinker compared to ligaments [17].

The bone-tendon/ligament interface, also called the osteotendinous junction, is composed of a gradual interface between tendon and bone spanning four zones (Fig. 1): a dense TL zone; non-calcified fibrocartilage; calcified fibrocartilage; and bone [18,19]. The same collagen bundles from the tendon region gradually intermesh with non-calcified fibrocartilage, which range from 150 to 400 μm in width. The non-calcified fibrocartilage zone contains collagen types II and III, with lesser amounts of types I, IX and X, as well as the proteoglycans aggrecan and decorin [20,21]. The fibrocartilage then becomes progressively calcified and continues into the adjacent cortical bone [22]. The bone zone contains ~40% by volume of type I collagen and ~50% by volume of carbonated apatite mineral, which provides stiffness [21]. The tendon insertion region, bone, and calcified fibrocartilage show specific microstructural properties, including a strong anisotropy and

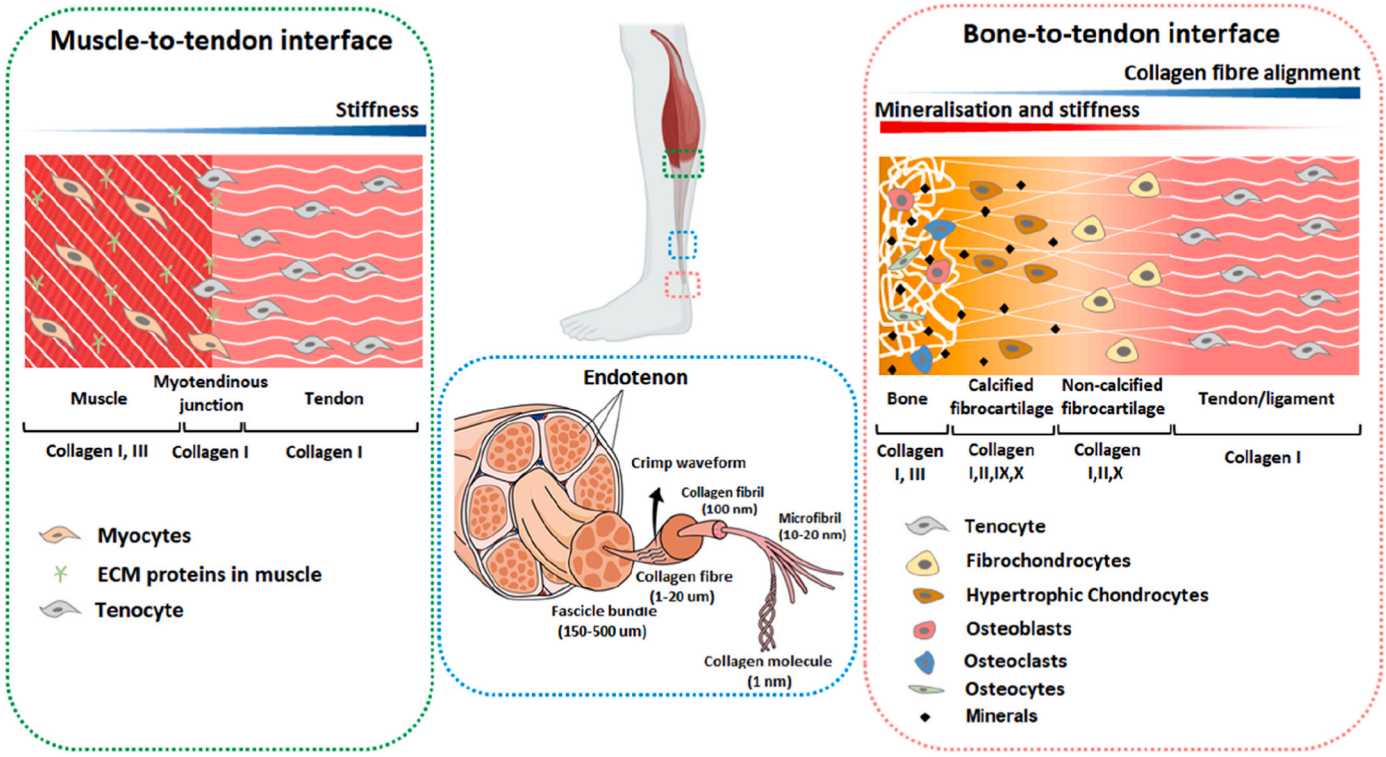


Fig. 1. Dashed blue box: the multi-unit hierarchical structure of TL is composed of collagen molecules, fibrils, fibre bundles, fascicles and TL units that oriented along TL's axis; dashed red box: tendon-bone interface includes gradients of mineral content, stiffness, fibre alignment, as well as cell variety; dashed green box: the aligned collagen fibres in tendon to muscle at oblique direction. Various ECM proteins present at interface and muscle side.

interdigitations, which might be linked with the loading environment [23].

The area where the tendon inserts into muscle is called the myotendinous junction or muscle-tendon junction (MTJ), and it is here where force is transferred from muscle to tendon [24]. Collagen VI is present in the endomysium extending to the MTJ. On the muscle side, the basement membranes are mainly composed of collagen IV [25] and fibrillar types I and III predominate in adult endo-, peri-, and epimysium fibril forming collagens in the skeletal muscle [26,27]. Collagen XXII was only observed at MTJ, while all the other collagen types are abundant at the MTJ and in muscle perimysium or endomysium [28].

2.2. Biomechanics

With multiple hierarchical levels to TL structure, there is meaningful scope for varying its local extension and sliding mechanics, and consequently whole TL biomechanical behaviour, through minor adjustments to the composition at one or more of the hierarchical levels of the tissue. TL mechanics are affected by both loading direction and anatomical location [29]. Collagen is a stiff structural protein, providing tissues with tensile strength. As such, the aligned collagen fibres along the long axis make the tendon a highly anisotropic tissue, particularly well suited to the uniaxial tensile strain transferring role of the tissue [30]. Typical stress-strain curve for tendon (Fig. 2A) or ligament (Fig. 2B) consists of three regions [31]. In the *"toe"* region, the collagen crimps are removed by stretching, followed by straightening at molecular level in the *"heel"*, and then, in the *"linear"* region, the collagen fibres have straightened out. Finally, the tears occur, and the tissue can fail unpredictably in the *"failure"* region [31–33]. Mechanical strength of TL tissues is influenced by the crimp pattern [34]. The linear region is typically up to 4% strain, where tendons undergo elastic deformation. Beyond 4% strain, microscopic failures are known to occur, and beyond 8–10% strain, macroscopic failure occurs [35].

Rate of loading has been shown as an essential factor in TL rupture, especially when the loading is applied quickly and obliquely [35,36]. Mechanical properties are also highly influenced by the thickness and collagen content of the tissues, which means several factors like age, species, and tissue type indirectly affect the tensile strength and failure point of TL. For instance, the range of failure stresses may vary in tendons from the 24–69 MPa of the patellar to the 112 MPa of the gracilis, and in ligaments from the 1–15 MPa of the flavum to the 24–46 MPa of the lateral collateral [31]. The mechanical properties of native tendon, ligament, muscle, BTJ and MTJ are listed in Table 1.

The bone-tendon unit (BTU) exhibits gradients in mineral content and collagen orientation, which likely act to minimise stress concentrations. The progressive increase in mineral proportion in the interface toward the bone is correlated with an increase in stiffness, resulting in a continuing decrease in the strain away from this region. However, the elastic modulus was found to be as twice as high in the calcified fibrocartilage as in the uncalcified fibrocartilage, in correspondence with the growth in mineral content [43].

Due to the different functions of muscle and tendon compared to tendon and bone, their mechanical properties are also dissimilar. Muscle tissue, which is highly compliant, generates force that is to be transferred across a joint to incite joint movement. Tendons function as the link that transfers force exerted by the muscle to its target insertion, which requires its high stiffness value. These tissues respond to stresses with different strain behaviours as a result of these stiffness differences [44]. The MTJ serves as an interface to decrease stress-concentrations and failure at this junction. Muscle will show a higher strain than tendon to a given stress, while MTJ will have a strain in-between the two [41]. The loads applied to a muscle-tendon-bone unit during active contraction create a uniform tension across the structure. However, the difference in the mechanical, structural and compositional

Table 1
Mechanical properties of the native tendon, ligament muscle, BTJ and MTJ.

Tissue	Type	Young's Modulus (MPa)	Ultimate tensile strength (MPa)	Strain at failure (%)	Ref
Bone	Human bone (Cortical)	18203	–	–	[37]
BTJ	Animal BTJ (Mice)	~ 2000-3000	30–60	4–5	[38]
TL	Human Achilles tendon	819	79	8.8	[39]
	Human ACL (16–26 years)	111	37.8	60.25	[40]
	Human ACL (48–86 years)	65.3	13.3	48.5	[40]
	Animal ACL (young adult monkey)	186	66.1	60	[40]
	Animal tendon (pig)	500–1850	52–120	5–16	[41,42]
MTJ	Animal MTJ (pig)	0.2789	0.1478	122.4	[41]
Muscle	Animal Muscle (pig)	0.005–2.8	–	–	[41,42]

BTJ: bone-tendon junction; TL: Tendon/ligament; MTJ: muscle-tendon junction; ACL: anterior cruciate ligament.

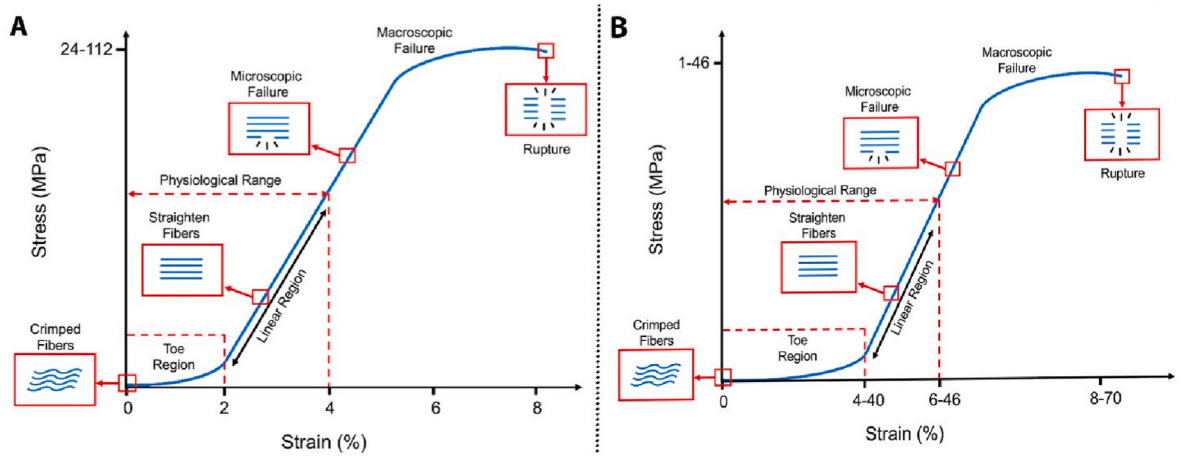


Fig. 2. Typical stress–strain curve and schematization of the behaviour of the collagen fibres for tendons (A) and ligaments (B). Typical ranges of stress and strain are indicated on the x and y axes. Reproduced with permission from Ref. [31].

characteristics of BTU and MTU protect them from mechanical damage thorough facilitating force transfer from tendon to muscle/bone during movement [45].

Thus, the complex structure and biomechanical interplay of tissue components results in a region that is difficult to engineer replacements for. Various biopolymers, both synthetic and natural, have been employed for regeneration of tendon/ligament and their interfaces.

3. Biopolymers

Absorbable biopolymers have been explored for tissue healing and regeneration. Both natural and synthetic absorbable biopolymers, including their different blends and composites, have become prominent in a range of biomedical applications, demonstrating suitability for tissue engineering approaches.

3.1. Natural biopolymers

Natural biopolymers, such as collagen, gelatine, silk, and hyaluronic acid, are widely used for tissue engineering TL and their interfaces, since they facilitate cell attachment, differentiation and mimic the native ECM. Although natural biopolymers are more biocompatible and biofunctional than synthetic biopolymers, there are challenges in fabricating regenerative scaffolds due to their poor tensile properties.

Collagen. Collagen is one of the key structural proteins found in the extracellular matrices of many connective tissues in mammals [46]. There are at least 16 types of collagen, but more than 80% of the collagen in the body includes types I, II, and III. The common choice for TL tissue regeneration is collagen type I since it is prevalent in the native TL and creates the connective tissue on which the TL fibroblast cells adhere and proliferate [47,48]. It was shown that collagen scaffolds with mechanical stimulations can promote tenogenesis, cell orientation and collagen content for tendon regeneration [49,50]. Collagen is also known to be more biocompatible than other biopolymers because of its surface activity, biodegradability, and nontoxicity [51].

Collagen has been mainly combined with other polymers for TL tissue engineering. For example, electrospun poly(caprolactone) (PCL) scaffold was coated with collagen to promote cell attachment and vascularization for ACL tissue regeneration [52]. Collagen coating coupled with mechanical stimulation can promote TL regeneration. For instance, aligned electrospun poly(L-lactic acid) (PLLA) fibres coated with type 1 collagen showed synergistic effect on tenogenic differentiation of human mesenchymal stem cells (hMSCs) [53].

Collagen-derived sponges were also used alongside a knitted scaffold for ACL repair, which resulted in reduced inflammation compared to scaffolds without collagen [54,55]. Collagen membrane were also used to wrap braided scaffolds to sustain release of basic fibroblast growth factor (bFGF) used in regeneration of bone-ACL-bone unit [56]. Moreover, the collagen wrapping isolated the scaffold from the synovial fluid inside the joint cavity [56].

However, collagen has great potential to be directly used as a scaffold. Multilayer collagen-based scaffolds were prepared by freeze-drying for bone-tendon tissue regeneration [57] with scaffolds exhibiting gradual transition in microenvironment and mechanical properties, and supported cell attachment and proliferation of human osteoblasts, fibroblasts and chondrocytes [57]. In another study, a core-shell tendon scaffold based on collagen and elastin was prepared by combination of two different components (Fig. 3A): a non-porous and load-bearing core component developed by braiding collagen/elastin-based membranes and a highly porous, hollow shell component (Fig. 3B and C) [58]. While both core and shell components showed good cytocompatibility *in vitro*, the porous shell structure directed cell orientation and growth within scaffold [58].

Gelatine. Gelatine is another protein-based natural biopolymer, which is commercially available in two different types of gelatine (type A & type B) [59]. The appealing advantages of gelatine, such as its high biocompatibility, low antigenicity, cell-adhesive structure, and modifiability with diverse functional groups (for coupling with cross-linkers and ligands), have made it an attractive biomaterial for TL tissue engineering [60]. For instance, methacrylated gelatine was co-electrospun with PCL to mimic the cellular characteristics of the native tendon [61]. Human adipose derived stem cells (hASCs) were impregnated into

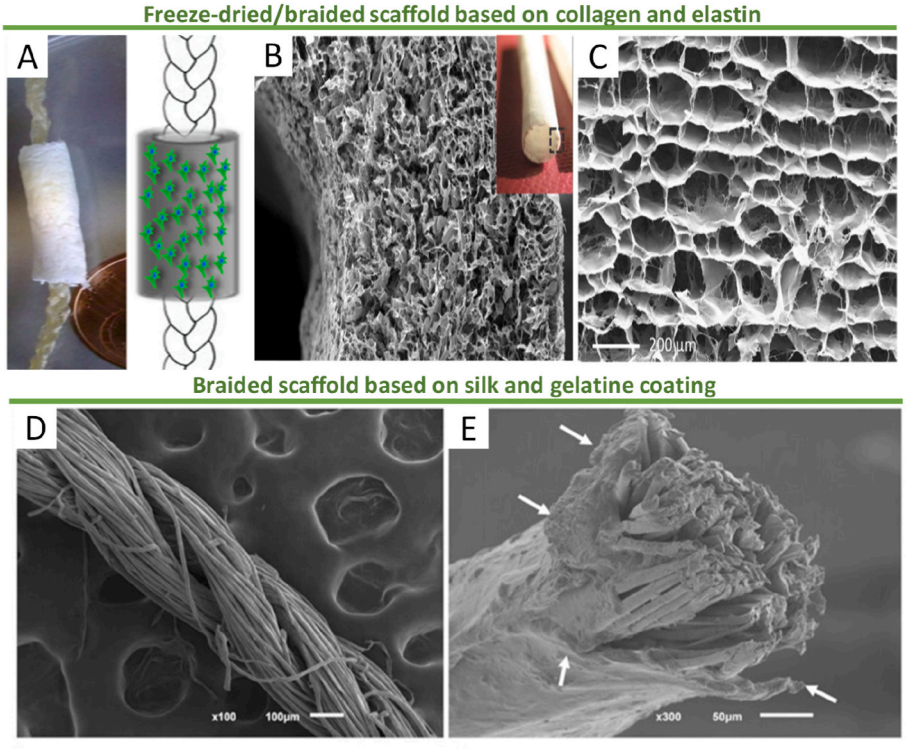


Fig. 3. Examples of TL scaffolds based on different natural biopolymers. (A). Image of the collagen/elastic-based core-shell scaffold with a schematic representation; (B) Micro and macro (insert) structure of the hollow shell component; (C) Axial view of the shell porosity including an anisotropic axial porosity to alien the cells. Reproduced with permission from Ref. [58]. (D, E) Scanning electron microscope (SEM) images of silk suture threads for tendon repair, uncoated suture (D) and suture threads coated by gelatine-based hydrogels containing tendon cells (E). The Arrows show the gelatine covering the core fibre. Reproduced with permission from Ref. [63].

the electrospun photo-crosslinked scaffold to generate a cell-laden construct and were observed to orient along the fibres [61].

Gelatine with/without cells was also used as the coating of fibrous scaffolds in TL tissue engineering [62,63]. The non-absorbable silk suture threads coated with gelatine-based hydrogels containing human tendon derived cells (hTDC) (Fig. 3D and E) generated a collagen-rich structure that was comparable to native tendon tissue [63]. The encapsulated cells migrated and proliferated within the hydrogel and aligned at the surface of the core thread. In another study, gelatine hydrogel was used with braided PLLA scaffold to control the release of bFGF, resulting in improved collagen production, osseointegration, intra-scaffold cell migration, and vascularization in bone-ACL-bone unit of a rabbit model after 8 weeks implantation [56].

A porous synthetic suture tape was also coated by a chitosan/gelatine hydrogel, which is crosslinked by tannic acid. This hydrogel coating of the suture tape resulted in a 332% increase in pull-out force from the tendon, showing potentially decreased re-tear rates. *In vivo* experiments (mice models) indicated that the suture could not only reduce inflammatory index but also promote collagen and blood vessel generation. Although the collagen formation was mainly caused by the gelatine-based hydrogel, the anti-inflammatory behaviour was related to biological activities of tannic acid [64]. Also, gelatine-based bioinks, containing muscle and tendon cells, were employed to fabricate complex 3D printed muscle-tendon junction scaffolds [65] where the gelatine-based bioinks enabled the expression of the muscle- and tendon-specific proteins for the muscle and tendon sides, receptively.

Recently, Gelatin methacryloyl (GelMA) scaffolds have been used a Kartogenin (KGN) carrier with a bone marrow–stimulating technique for the repair of rotator cuff tear in rabbit models [66]. KGN was selected since it can promote selective differentiation of bone marrow mesenchymal stem cells (BMSCs) into chondrocytes [67]. Enthesis healing was evaluated over 12 weeks by using the KGN-loaded GelMA hydrogel scaffold with or without BMSCs. Although the GelMA was sufficiently crosslinked by UV irradiation, nearly 81% of the KGN was released within 12 h, caused by the generally high swelling and degradation rates of Gelatine-based hydrogels. However, the KGN-loaded GelMA hydrogel scaffolds with bone marrow stimulation enhanced healing tendon-to-bone insertion, identified by more fibrocartilage formation and better mechanical properties [66].

Silk. Silk is a protein spun into fibres by some lepidoptera larvae such as silkworms, spiders, mites and flies, and has been widely used in manufacturing and engineering [68]. Unlike the other natural biopolymers, the high tensile properties of silk fibres have been considered in scaffold fabrication for TL and interface regeneration [69]. For instance, the silk fibres were braided with hierarchical structures for ACL tissue regeneration and tested in a sheep model over 12 months resulting in the ingrowth of newly formed tissue and degradation of the silk fibres [70].

Microporous silk scaffold was prepared by combining a knitted silk mesh with freeze-dried silk sponge for *in vivo* reconstruction of ACL–bone insertion in a rabbit model [71]. Although the histology data were promising, the maximum load of the regenerated ligament (24.59 $\pm$ 1.64 N) was far from that of the native ACL (131.82 $\pm$ 17.64 N) after 24 weeks implantation [71]. The silk fibroin scaffold was fabricated by freeze-drying and salt leaching techniques [72]. The scaffolds were designed with an anisotropic pore alignment in correspondence with bone and tendon sides to repair bone-tendon insertion. Furthermore, 3D silk fibroin scaffolds resulted in high tenogenic differentiation of mesenchymal stem cells (MSCs) and tensile properties through dynamic mechanical stimulation culture conditions for tendon tissue engineering [73].

A silk-collagen scaffold with both ends functionalised by hydroxyapatite was recently used to investigate osteointegration at the ACL-bone interface in a rabbit model [74]. The combination of silk and a collagen sponge mimicked the natural biocomposition and structure of ligament extracellular matrix (ECM) and revealed acceptable cellular infiltration and tissue regeneration. However, the induced hydroxyapatite resulted in the massive formation of more mature bone at the tendon-bone interface [74].

Hyaluronic acid. Hyaluronic acid, or hyaluronan, is another natural choice for ligament regeneration [75]. The unique viscoelastic nature of hyaluronic acid, along with its biocompatibility, cellular adhesion and proliferation, non-immunogenicity as well as anti-inflammatory character, could enhance TL tissue regeneration [76,77]. However, the hyaluronic acid gel degrades quickly, which requires chemical modifications to enhance processability and biodegradation [75].

Hyaluronan-based coating on electrospun PCL scaffolds enhanced the electrostatic bonds between proteins and ECM, resulting in better protein adsorption on the surface of the nanofibres for ligament regeneration [78]. In other work, the generation of dense collagen type I fibres was achieved by using hyaluronan-based fibrous scaffolds fabricated through wet-spinning [79]. Electrospun core–shell nanofibers of poly (l-lactic acid)-hyaluronic acid (PLLA/HA) were also evaluated for pelvic ligament tissue engineering *in vitro* in presence of mouse bone marrow-derived mesenchymal stem cells (mBMSCs). The core–shell nanofiber showed high expression gene markers including type I collagen, type III collagen, and tenascin-C [80].

Hyaluronic acid has also been used to controlled release of growth factors for TL tissue engineering. For instance, PCL electrospun scaffolds, consisting of random and aligned nanofibers, were coated by hyaluronic acid to achieve sustained release of growth factors from platelet-rich plasma (PRP) [81]. The combined effects of growth factor release and fibre alignment leads to enhanced tenocyte cell proliferation rates, as well as upregulated expression of type I collagen, type III collagen, tenascin-C and biglycan [81].

3.2. Synthetic biopolymers

The most widely used synthetic biopolymers in TL and interface tissue engineering is the family of linear aliphatic polyesters: polylactide (PLA), poly (glycolic acid) (PGA), poly (lactide-co-glycolide) (PLGA), PCL, and poly (*para*-dioxanone) (PPDO). In general, they all exhibit several advantages linked to large-scale manufacturing, ease of processability and reproducibility, good mechanical properties, controlled degradation, limited disease transmission, biocompatibility and FDA-approval for certain clinical use in humans. However, each of synthetic biopolymer exhibits specific properties that enhance or limit its use in certain tissue engineering applications.

Poly (lactic acid). Poly (L-lactic) acid (L enantiomer of PLA, (PLLA)) has excellent mechanical properties and biocompatibility that make it more appropriate for load-bearing applications, especially for tendon, ligament, and tendon/ligament-bone interface scaffolds. However, this biopolymer also has several drawbacks for this application, including slow degradation rate, poor ductility and hydrophobicity [82]. PLA should be blended or copolymerized with other lactic acids [83], glycolide [84] or ε-caprolactone [85] to moderate the limitations.

PLLA scaffolds have mostly been fabricated through electrospinning, braiding and knitting techniques [8]. PLLA nanofibres were electrospun with mechanical, structural and biocompositional gradients to mimic the bone-tendon interface [86]. The random-aligned-random nanofibres, immobilized PDGF and mineral deposition mainly resulted in corresponding strength, tenogenic and osteogenic differentiation of ADSCs, respectively [86]. The PLLA fibres were also braided to fabricate tendon scaffolds with superior mechanical properties and combined with natural biopolymers to improve biological responses [87]. For example, PLLA braided fibres were combined with the collagen membrane for sustained release of basic fibroblast growth factor (bFGF) to provide a complex scaffolding system for mechanical and biochemical signaling in regeneration of bone-ACL-bone unit in rabbit models [56]. The knitted PLLA fibres were also employed in regeneration of the medial collateral ligament (MCL) in a rabbit model, resulting in type I collagen expression and fibrocartilage formation 16 weeks

post-implantation [88].

PLLA electrospun nanofibres were also used to fabricate hierarchical scaffolds for TL regeneration by Sensini et al. [89]. Biomimicking PLLA scaffolds were fabricated by assembling multiple bundles and wrapping in a sheath of nanofibres to obtain a compacted hierarchical structure, similar to the native TL. The hierarchical scaffold exhibited tensile properties in the range required to replace TLs. Although the seeded scaffold with fibroblasts resulted in cell orientation and positive metabolic activity over time, *in vivo* animal studies must be conducted to provide stronger indications for the biomimicking capability of the scaffold [89].

Poly (glycolic acid). Poly (glycolic acid) (PGA) has greater strength and hydrophilicity than PLA, and a self-reinforced form of PGA is significantly stiffer than any other form of clinically applicable biopolymer, which could be considered for the bone side of tendon/ligament-bone unit scaffolds [90]. However, PGA degrades rapidly which is not desirable in TL scaffolds. The high concentration of the degradation product, glycolic acid, may also cause an increase of the localized acid concentration which will result in tissue damage [91]. PGA braided scaffolds were seeded with rabbit ACL cells for ligament tissue engineering, however, the rapid degradation of the PGA scaffold during 7 days was found detrimental to ECM formation [87].

Poly (lactic-co-glycolic) acid. Poly (lactide-co-glycolide) (PLGA) copolymers provide excellent control of degradation rate, compared with its constituent homopolymers PLA and PGA, by changing the ratio between its monomers and consequently governing the crystallinity and hydrophilicity [92]. Pure PLGA exhibits poor hydrophilicity and sub-optimal mechanical properties and bioactivity, which limits clinical applications, especially in bone and tendon/ligament regeneration. Therefore, PLGA is usually blended with other biomaterials, such as bioactive glass and ceramics or other aliphatic polyesters like PLA [93,94]. PLGA is typically electrospun for TL tissue regeneration applications [95–97].

Electrospun PLGA nanofibres containing basic fibroblast growth factor (bFGF) on top of knitted silk microfibres were used to mimic native ECM structures and improve the mesenchymal progenitor cell

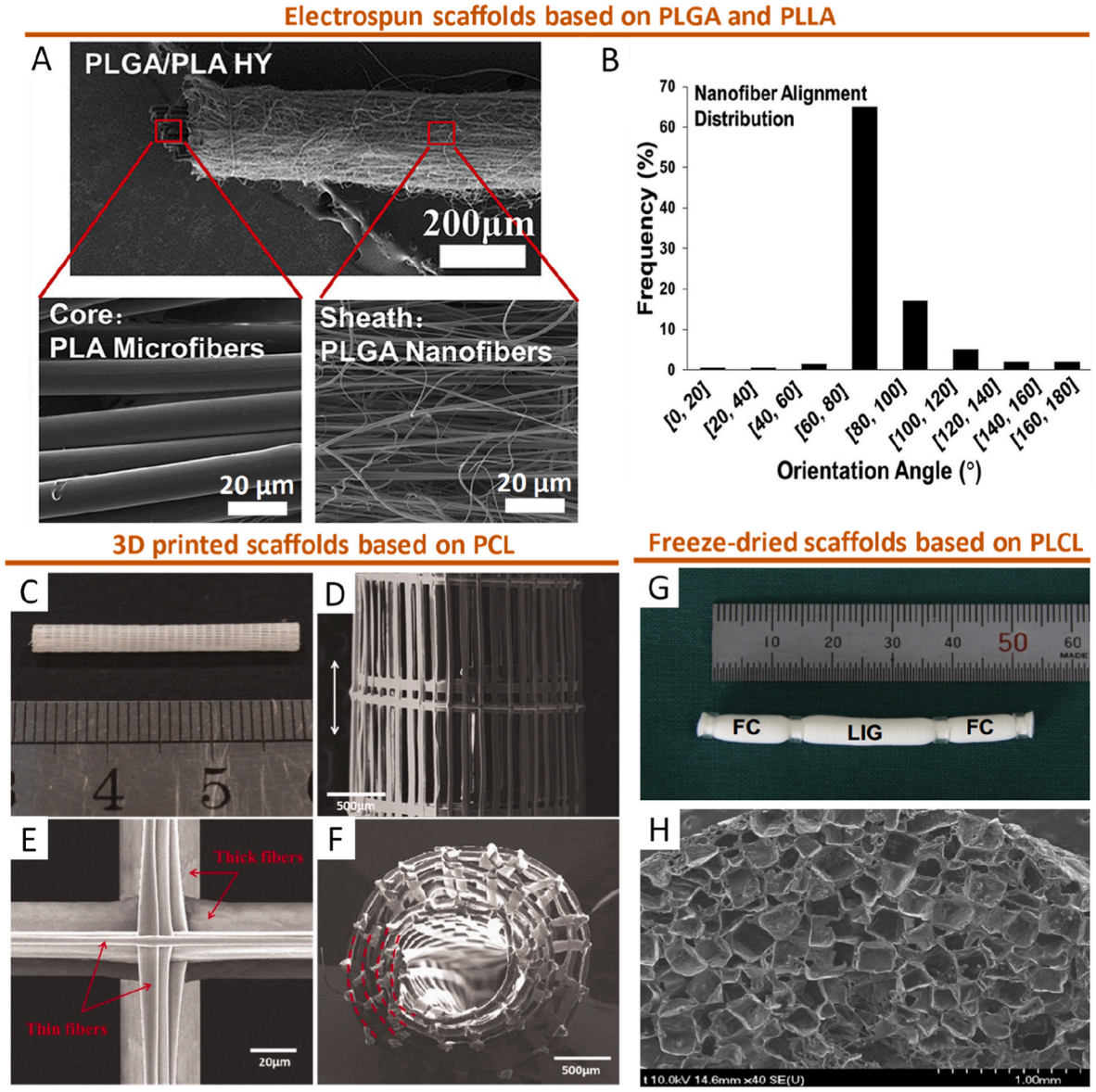


Fig. 4. Examples of TL scaffolds based on different synthetic biopolymers. (A) PLGA/PLA nanofibre/microfibre hybrid yarns; (B) Fibre diameter distribution of PLGA nanofibres on the surface of PLGA/PLA hybrid yarns. Reproduced with permission from Ref. [98]. (C–D) different views of tubular PCL scaffold composing of thin and thick fibres for tendon tissue engineering. Reproduced with permission from Ref. [105]. (G–H) Cylindrical porous PLCL scaffold designed for the ligament–bone interface tissue regeneration. Reproduced with permission from Ref. [111].

proliferation and attachment [95]. PLGA nanofibres were also electrospun in an aligned-to-random orientation to remodel the native tendon-to-bone interface tissue through gradients of mechanical and structural properties [96]. PLGA nanofibres were also electrospun on top of PLA microfibres, as shown in Fig. 4A and B, to promote tenogenesis of adult stem cells and to mimic the aligned fibril structure in the native tendon [98]. The highly aligned PLGA nanofibres not only improved the tensile strength but also increased cell orientation along the longitudinal direction of the nanofibres [98].

Poly (ε-caprolactone). Poly (ε-caprolactone) (PCL) is also a biocompatible and semi-crystalline aliphatic polyester which is bioresorbable and non-toxic for cells or living organisms, and so it has been widely used in tissue engineering and drug delivery [99–101]. Unlike PGA and PLA, PCL is a ductile polymer with lower tensile strength and Young modulus but higher elongation at failure. PCL degradation is also three times slower than PLA, which can limit its use as a biodegradable tendon/ligament scaffold. Therefore, PCL has been blended or copolymerized with different ratio of PLA to improve the mechanical properties, shape memory ability, hydrophilicity as well as biodegradability [91,102].

PCL-based scaffolds have been mainly electrospun for tendon and ligament application [61,78,103]. For example, the fibrous PCL scaffolds were fabricated by co-electrospinning of aligned microfibres and random nanofibres of PCL to create a hybrid scaffold for ligament regeneration [78]. PCL was also electrospun with methacrylated gelatine to improve the biological responses of the seeded human adipose-derived stem cells to the growth factors [61]. PCL scaffolds were electrospun into 2D and 3D structures, including 2D random sheets, 2D aligned sheets and 3D bundles, to study the merits of the architecture of 2D and 3D scaffolds for tendon repair [104]. The findings showed that aligned fibres guided tendon fibroblasts in the parallel orientation and the 3D scaffolds were superior to the 2D scaffolds because of their higher tensile strength. The 3D scaffolds also structurally resemble the native tissue more closely. However, the tensile strength of the 3D scaffolds did not mimic native tendons, which could be improved by adopting braiding techniques or/and engineering the material's properties [104].

Tubular multilayered PCL scaffold (Fig. 4C–F) was developed by electrohydrodynamic jet printing thick fibres as structural support and thin fibres as potential cues for aligning cells [105]. The E-jetted scaffold involved fibrous bundles with interconnected spacing and geometric anisotropy along the longitudinal direction of the scaffold. The thick fibres, as the supporting layer, improved the stability and mechanical strength of the scaffold. Furthermore, the scaffolds aligned human tenocytes along the longitudinal direction of the scaffold [105]. In a different approach, PCL microfibrous scaffolds for bone-ligament-bone (BLB) regeneration were fabricated by melt electrowriting technique to engineer and control the structure of the scaffold through predetermining microfibre deposition [103]. Other types of PCL scaffolds were also integrated with different growth factors, such as PDGF-BB [106], BMP-2 [106], FGF-2 [107], to control the differentiation of stem cells in the BTJ by biochemical signaling.

Poly(L-lactide–co-ε-caprolactone). Poly(l-lactide–co-ε-caprolactone) is a biodegradable co-polymers of ε-caprolactone and L–lactide, which has been of great interest for biomedical applications [108]. PLLA is a stiff and brittle polymer, while PCL has rubbery properties with slower degradation rate than PLLA. PLCL copolymer shows high flexibility and elasticity with excellent recovery under cyclic mechanical strain in culture media [109]. PLCL has been used as a scaffold in tissue engineering for tendon, ligament, and bone-tendon interfaces [110,111].

Porous PLCL scaffolds were fabricated by extrusion–salt-leaching method and seeded with tenocytes in a dynamic tensile stimulation system [110]. The degradation of the PLCL scaffold was relatively slow; however, cells accelerated the degradation of PLCL during culture. The elastic behaviour of PLCL was beneficial in dynamic tensile stimulation systems since the polymer could retain the original shape perfectly without any deformation under cyclic loads [110]. In other work, a similar porous PLCL scaffold was used in designing a ligament–bone interface scaffolds including a heparin-based hydrogel for local delivery of cells/BMP-2 [111]. The PLCL scaffold was composed of fibrocartilage (FC) or ligament (LIG) regions (Fig. 4G–H), which could isolate the cells and growth factor into each designated region by using heparin-based hydrogel [111].

Polydiaxanone. Poly (para-dioxanone) (PPDO) is another biodegradable polyester used in both hard and soft tissue engineering due to its exceptional mechanical properties, high biodegradability, bioabsorbability and biocompatibility. PPDO is widely used in industrial production of surgical sutures, because of its exceptional mechanical flexibility and bioabsorbability [112]. However, because of the rapid loss of mass and mechanical strength during degradation, PPDO is not suitable for applications in tendon, ligament, and tendon/ligament-bone interface scaffolds [113]. However, PPDO could be considered in vascular, muscle and myotendinous junction tissue engineering based on its mechanical flexibility and biodegradability [114].

PPDO sutures (or commercially named PDS sutures) have been used to repair different tendons, such as Achilles tendons [115,116] and flexor tendons [117,118]. PPDO sutures show acceptable results in tendon grafting; however, the outcome depends on suturing techniques [115,117]. Furthermore, the PDS monofilament sutures show higher maximum load and fewer ruptures compared to PDS threads in Achilles tendon repair [115]. However, unlike monofilament PPDO sutures, multifilament electrospun PPDO sutures resulted in neovascularisation and densely cellular infiltration *in vivo* study on sheep models [119].

Continuous electrospun PPDO filaments were produced by electrospinning the PPDO fibres on a wire guide to form sub-microfibres in a dense and narrow mesh, that can be detached as a long and continuous thread [120]. The thread then was stretched and used to create multifilament yarns which can mimic the hierarchical architecture of native TLs. The safety of the electrospun yarn was evaluated *in vivo* using a rat model over 20 weeks. The scaffolds showed a good safety profile with mild foreign body reaction and complete degradation within 5 months after implantation, which is related to high acidic by-products form PPDO hydrolytic degradation [120]. Later, the same method was used to develop multi-layered scaffold from electrospun sheets to heal bone-tendon junction in the rotator cuff. The multi-layered PPDO scaffolds showed a maximum suture pull out strength of 167 N, closely matching human rotator cuff tendons [121].

3.3. Hybrid composites

Both natural and synthetic biopolymers have been employed for TL and interface tissue engineering applications. Table 2 shows the advantages and disadvantages of the most commonly used synthetic and natural biopolymers used in TL and interface regeneration. While the main advantage of synthetic biopolymers is mechanical strength, the natural biopolymers are basically privileged by biomimicking ECM properties. Hence, many different hybrid biopolymers have been developed to benefit from the advantages of both naturals and synthetics as the sole composite/blend.

Most of the hybrid composites have been developed for electrospun scaffolds in TL tissue engineering, mainly because mixing materials in a solvent and electrospinning the solution is a cheap and accessible method. In addition, PCL, PLA and PLGA are the most common synthetic biopolymers blended with natural biopolymers, mostly collagen, to promote biocompatibility and biofunctionality of electrospun TL scaffolds [41,95,131,132]. For instance, crosslinked PLLA/Collagen blends (PLLA/Coll-75/25, PLLA/Coll-50/50) were electrospun into aligned nanofibres and then wrapped in bundles to mimic the structural and mechanical properties of native TLs [133]. PLLA/Coll-75/25 showed more desirable mechanical properties after ageing in PBS for 14 days, compared to the PLLA/Coll-50/50.

PLLA was blended with collagen and then electrospun to form

Table 2
Advantages and disadvantages synthetic and natural biopolymers for the regeneration of tendon/ligament and their interfaces.

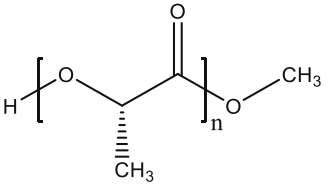
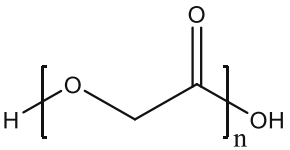
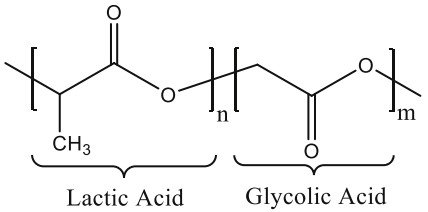
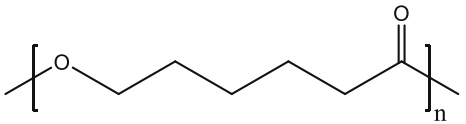
Biopolymer category	Advantages	Disadvantages
SYNTHETIC	PLLA: 	
	Better cell adhesion than PCL, PGA or PLGA [76]; slow degradation rate (1–4 years) [122]; FDA approved and good processability [123]	Acidic degradation [76]; high mechanical stiffness, and low toughness for muscle-tendon interface tissue engineering scaffolds [123]; low biological properties such as cell attachment [124]; hydrophobic surface [123]
	PGA: 	
	Good processability and FDA approved material [76]; high stiffness for bone side of TL-bone interface tissue engineering scaffolds [76]	Rapid (6–12 months) and acidic degradation [125]; low biological properties such as cell attachment [124]; high mechanical stiffness, and low toughness for muscle-tendon interface tissue engineering scaffolds [123];
	PLGA: 	
	Good processability; degradation rate can be tailored by changing the ratio of PLA:PGA [76]; FDA approved [123]; Suitable tensile properties for TL-bone tissue engineering scaffolds [76]	Acidic degradation [125]; low biological properties such as cell attachment [124]; high mechanical stiffness, and low toughness for muscle-tendon interface tissue engineering scaffolds [123];
	PCL: 	
	Good processability and FDA approved [124,125]	Very slow degradation rate [125]; highly elastic with low mechanical stiffness; very hydrophobic surface [126]; low biological properties such as cell attachment [124]
NATURAL		

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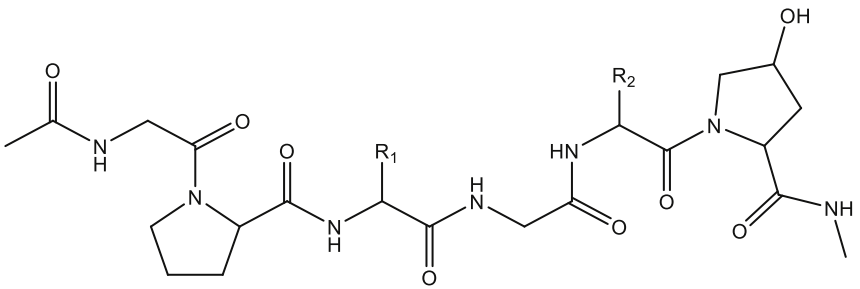
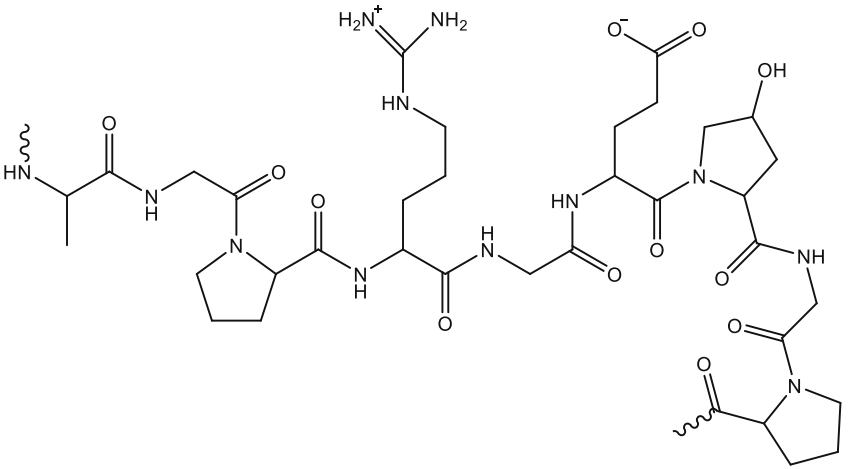
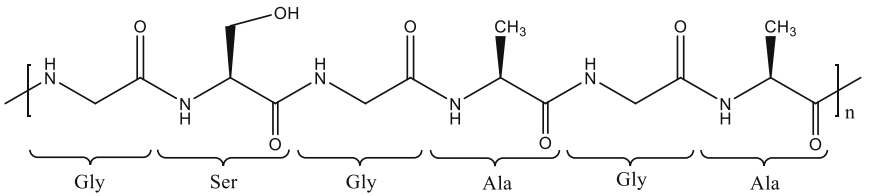
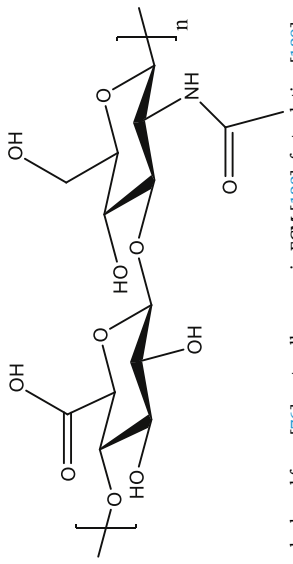
Table 2 (*continued*)

Biopolymer category	Advantages	Disadvantages
Collagen: 	Major component of tendons and ligaments [125]; Good cell recognition [126]; low antigenicity, good cell adhesion, biological signaling [124]	Poor mechanical strength [76]; risk of immunogenicity [127]; fast degradation [125,128]; low tensile and compressive properties [124]
Gelatine: 	Cheaper than collagen; anti-thrombogenic [123]; good cell recognition [126]; promotes cell adhesion [129]	Poor mechanical properties; unstable without modification and cross-linking [123,129]
Silk fibroin: 	Good mechanical properties; slow rate biodegradation [130]; loses its strength after 1 year, *in vivo* [122]	Limited cell adhesion [125]

(*continued on next page*)

Table 2 (*continued*)

Biopolymer category	Advantages	Disadvantages
Hyaluronic acid: 	Can be in sponge or hydrogel form [76]; naturally occurs in ECM [123]; fast gelation [129]; no immunogenicity, good cell interaction [124]	High surface tension and viscosity make it hard to electrospun [123]; rapid degradation, poor mechanical stability [75]

bundles for remodelling the fascicles of the native Achille tendon (Fig. 5A–C) [131]. Although adding collagen improved cell (human-derived tenocytes) attachment and proliferation, the mechanical properties of the electrospun scaffolds were dramatically reduced *in vitro* due to the fast degradation of collagen [131]. Calcium phosphate silicate (CPS) ceramic was also added into PLLA to increase osteogenic activity in tendon to bone interface regeneration [134]. The PLLA/CPS films, with a volume ratio of 5/1, the improved collagen orientation and the formation of cartilage and bone after 12 weeks of implantation into rabbit models [134].

PCL has been also combined with collagen [41], gelatine [135,136], and hydroxyapatite particles [132] for tendon/ligament tissue regeneration applications. PCL/gelatine microfibres were wet-spun with or without hydroxyapatite particles (HAp) to fabricate the gradient scaffolds for tendon to bone interface regeneration (Fig. 5D–G) [132]. Although the presence of HAp led to less alignment of microfibres, the gradient mineral profile resulted in successful protein generations in correspondence with the tendon and tendon-bone interface and bone sections after 14 days seeding with hASCs [132]. This study shows the importance of both minerals and natural biopolymer in true regeneration of tendon/ligament tissues in junction with bones.

A hybrid composite of PCL, chitosan (CHT), and cellulose nanocrystals (CNC) were also used to fabricate the continuous and aligned electrospun nanofibre threads to remodel the nanoscale collagen fibrils grouped into microscale collagen fibres of the native ligament [137]. The threads were then assembled into woven hierarchical scaffolds. The PCL/CHT/CNC nanocomposite nanofibrous scaffolds reached tensile strength (39 ± 2 MPa) and Young's Modulus (541 ± 84 MPa) in the range of tendon tissue (5–100 MPa and 20–1200 MPa, respectively). Moreover, the expression of tendon-related markers (Collagen types I and III, Tenascin-C, and Scleraxis) were observed by both seeded human-tendon-derived cells (hTDCs) and human adipose stem cells (hASCs) [137].

The critical role of hybrid materials coupled with scaffold architecture was highlighted in recent work. Nanofibrous scaffolds, based on Gelatine/PEUU (poly(ester-urethane)urea) blends, were developed using electrospinning followed by a chemical crosslinking method [138]. The scaffolds possessed crimped nanofibres and welded joints to biomimic the native microstructure of tendon-to-bone insertion. A continuous translational interface was observed between the tendon and the bone using nanofibrous scaffold three months after rotator cuff repairing in rabbit models. The crimped nanofibre scaffolds not only mechanically matched the native tendon tissue, but also promoted enthesis regeneration by facilitating chondrogenesis [138].

The *in vitro* and *in vivo* studies using natural, synthetic, and hybrid biopolymers in TL, enthesis, and myotendinous junction regeneration are summarised in Table S1 (Supplementary File).

4. Biofabrication techniques and signaling strategies

To achieve the best outcome, biopolymers must be formulated with respect to the appropriate biofabrication techniques and signaling strategies. Several review papers comprehensively discussed the roles of biofabrication methods and signaling strategies in TL and interface tissue regeneration [6,8,18,139]. Here, we briefly outline how biopolymers affect biofabrication and signaling strategies.

4.1. Biofabrication techniques

Electrospinning is the most widely used technique for the fabrication of TL and interface tissue-engineered scaffolds. The capability of fibre development from nano to microscale and flexibility in choosing synthetic and natural biopolymers are key advantages of electrospinning. Electrospinning enables hierarchical scaffolds that mimic the native structure of TL tissue, from collagen fibrils (~100 nm) to fascicle bundles (150–500 μm). Electrospun scaffolds can be classified as simple

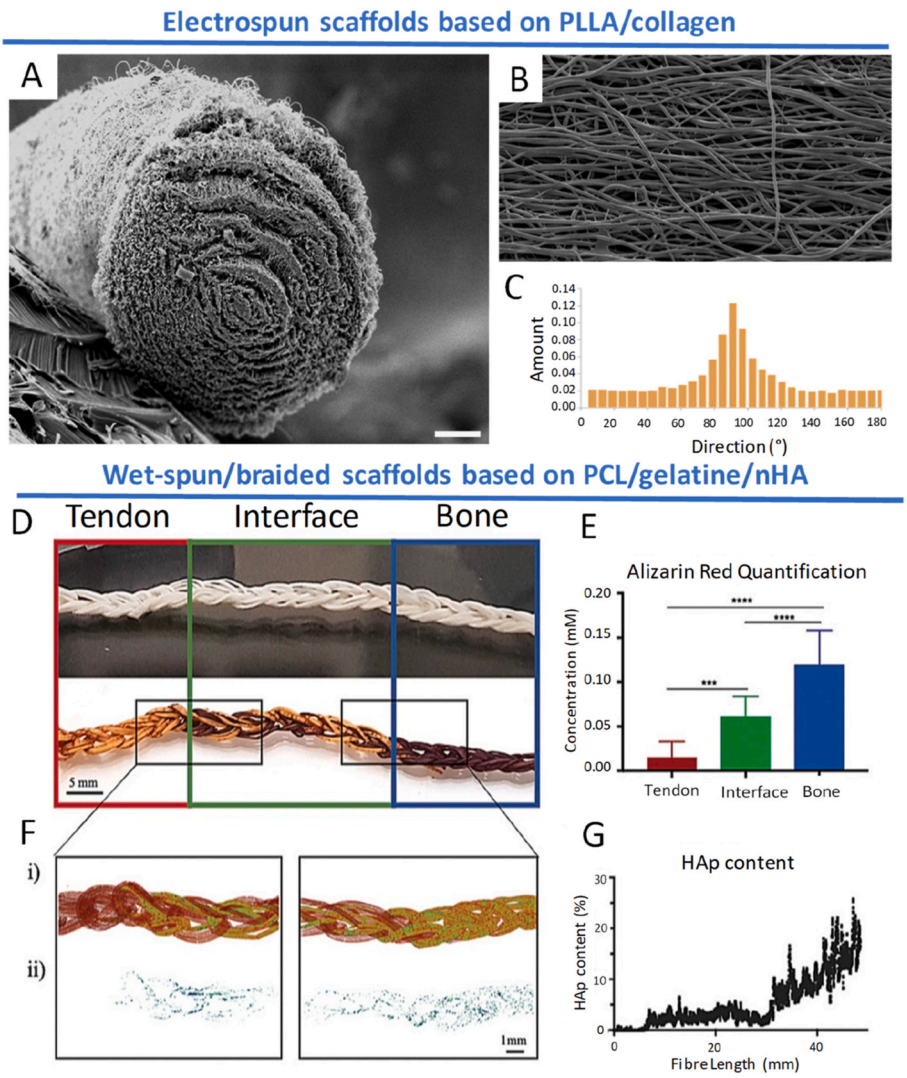


Fig. 5. Examples of TL scaffolds based on different hybrid biopolymers. (A) SEM image of the electrospun rolled scaffold made of aligned PLLA/collagen fibres; SEM image of the aligned fibres (scale bar = 50 μm) (B) and directionality histogram (C) of the scaffold showing the fibre alignment in the PLLA/collagen scaffold. Reproduced with permission from Ref. [131]. (D) Braided scaffold based on PCL/gelatine and PCL/gelatine/HAp microfibres to mimic tendon, interface and bone; (E,G) the gradient in HAp content in tendon, interface and bone parts of the scaffold. Reproduced with permission from Ref. [132].

mats, biphasic mats, multilayer mats or composite 3D structures, according to hierarchical complexity of the scaffolds [10]. Although multilayering and co-electrospinning became a common strategy to build the TL scaffolds, multiscale hierarchical 3D structures are essential for large tissue replacements to reproduce the entire hierarchical morphology of the native tissues [31]. Many different biopolymers have been electrospun to develop TL scaffolds, such as PCL [52,78,140,141], PLGA [96,142,143], PLLA [86,144], PPDO [145], PCL/gelatine blend [146], PCL/silk fibroin blend [147], PLCL/collagen blend [148], PLLA/collagen blend [131], PLLA/Poly(ethylene oxide)(PEO) blend containing an epigenetic inhibitor [149], PLGA/silk blend containing fibroblast growth factors [95], silk/collagen blend [150]. However, electrospinning biopolymer blends and composites mainly rely on toxic organic solvents, like chloroform and 1,1,1,3,3,3-hexafluoroisopropanol, which could be considered as a drawback of this method. Also, the mechanical properties of the electrospun matts are often lower than native TL tissue, which can reduce further for scaffolds based on hybrid biopolymers. Although blending synthetic biopolymers with natural polymers can be a good approach to enhance biocompatibility, the rapid degradation of the natural component may lead to a dramatic loss of mechanical integrity of the electrospun scaffolds. This highlights the importance of post-fabrication techniques in the sequence of electrospinning.

Braiding and knitting are mainly employed to convert spun fibres into 3D hierarchical scaffolds with the required strength for TL tissue regeneration. These techniques are essential to fabricate grafts for ACL repair, aiming to reach maximum mechanical strength from single fibers. Several biopolymers have been braided or/and knitted so far to develop TL grafts, like PLLA [56,87,88,144,151–154], PCL [152], PLGA [87,153,155], PGA [87], PLA-Pluronic copolymers [54,55], silk [70,156], and collagen/elastin [58]. Synthetic and silk fibres are often chosen due to their strength, accuracy, repeatability and ease of fibre development, while natural biopolymers are often employed as the coatings to improve cellular properties of the scaffolds. Braiding can limit the porosity of the scaffolds, which may result in an insufficient hydrogel coating for the fibres. This may reduce the efficiency of growth factors/cells, particularly when the designed cells/growth factors must be delivered to specific regions for TL interface tissue engineering.

Bioprinting has also been considered in the fabrication of TL scaffolds because of its capability to print living cells and therapeutic agents with hydrogels into complex constructs. The combination of 3D printed synthetic polymers as a support scaffold with bioprinted natural hydrogels were used to create complex scaffold systems for interface engineering [65]. However, bioprinted or 3D printed scaffolds cannot mimic the hierarchical structure of native TL tissues because of the typically large filament diameter [65,97]. Although both techniques benefit from predetermined filament deposition, bioprinting is restricted to hydrogels, and 3D printing is limited to thermoplastic synthetic biopolymers.

Other fabrication techniques like freeze drying,

electrohydrodynamic jet (E-jet) and wet spinning, and melt-electrowriting (MEW), have also been used for TL and interface tissue engineering, but less than electrospinning, braiding and knitting. Freeze-drying is can obtain tailored porous scaffold based natural biopolymers, like collagen and silk, to facilitate cell growth throughout the scaffold. However, the main weakness of freeze-dried scaffolds is poor mechanical strength [57,72,157]. E-jet and wet-spinning methods, like solution electrospinning, are based on organic solvents, which is not desirable due to potential toxicity [79,105]. In contrast, MEW offers a solvent-free biofabrication method with excellent control over scaffold architecture and porosity. It is a high-resolution biofabrication strategy that permits the accurate deposition of micrometre-scale fibres, enabling tunable mechanical properties, macro-porosities, and patterns [158]. However, MEW is limited to thermoplastic (synthetic) biopolymers, with PCL currently the 'gold standard' material [103,159,160].

4.2. Signaling strategies

Native TL tissue is characterized by a complex structural and biocomposition. Hence, mimicking their biofunctionality is achieved by signaling strategies to direct regeneration, mainly based on cell type or culture, biochemical molecules (e.g. growth factors), and mechanical stimulation.

Growth factors. The function of growth factors is to interact with and stimulate cell differentiation, migration and proliferation [6]. Growth factors play a critical role in TL interface tissue engineering; using several growth factors simultaneously has recently become a common strategy to modulate the activity of stem cells in different zones (e.g. bone, tendon or fibrocartilage) of multiphasic scaffolds [161,162]. This approach achieves a complex scaffold system closer to native TL junctions. However, there is still a long journey to translate this strategy to the clinic.

Basic fibroblast growth factor (bFGF) [95] (also known as fibroblast growth factor 2 (FGF-2) [163]), growth differentiation factor (GDF) [163–167], transforming growth factor-beta 3 (TGF-β3) [168], and platelet-derived growth factor (PDGF) [169,170] have been commonly used for TL tissue engineering [171,172]. Considering interfacial regeneration, several factors including transforming growth factor-beta 1 (TGF-β1) [173], TGF-β3 [173], different bone morphogenetic proteins (BMPs, e.g. BMP-12, BMP-7,BMP-2) [164,174–177], PDGF-BB [178], FGF-2 [179] and F2A (peptide mimetic of FGF-2) [172] have been used to signal stem cells for interfacial regeneration, in both *in vitro* and *in vivo* studies [8].

Cell types. Incorporating cells into the scaffolds aims to maintain the cells in the region where the damage has occurred, thus guiding tissue regeneration [180], with the addition of tenocytes and fibroblasts being a natural choice. However, stem cells are widely used, including tendon-derived stem cells (TDSCs) [181], mesenchymal stem cells (MSCs) [182], Adipose-derived stem cells (ADSCs) [183], bone marrow mesenchymal stem cells (BMSCs) [184], and iPSCs [185], that can differentiate into tenocytes or fibroblasts. Several studies have showed promising outcomes in tendon-to-bone regeneration and mechanical properties after transplantation of BMSCs [186,187].

Cell culture strategies. These strategies are effective and can be culture of MSCs alone, coculture of differentiated cells, or coculture of the differentiated cells together with MSCs. For instance, coculture of osteoblasts with fibroblasts [188] and myoblasts with fibroblasts [41] was adopted to mimic native BTJ and MTJ, respectively. A trilineage coculture system, including osteoblasts, bone marrow mesenchymal stem cells (BMSCs), and rabbit fibroblasts, was studied with in interaction with a silk scaffold [189]. Coculture strategies are challenging for TL interfacial tissue engineering because of the complexity of the cellular environment and tissue vascularization [139]. Therefore, using MSCs alone with controlled differentiation is another effective strategy as MSCs can differentiate into the various cell types if they are seeded in a graded scaffold with mechanical and biochemical stimulation [8]. For instance, the gradient of hydroxyapatite in aPCL/gelatin fibrous scaffold resulted in a graded differentiation of hASCs toward the osteogenic matrix, which can mimic the biocomposition of tendon-to-bone interface tissue [132].

Mechanical Stimulation. Mechanical stimulation can substantially influence the development of TL and their interface tissues [190–192]. TL tissue are frequently subjected to tension applied by muscular contraction or other external forces; therefore, mechanical loading is more popular to modulate the critical characteristics of the cells, such as cell differentiation and alignment, and matrix deposition [8,86,193]. It has been shown that dynamically loaded constructs are superior in regeneration of TL and interface tissues compared to static constructs [194]. Bosworth et al. [195] showed that dynamic loading over 21 days (with 3600 cycles per day) of cell-seeded PCL electrospun yarns not only increased the cell proliferation and tensile strength of the yarn but also resulted in the up-regulation of some tendon-related genes, such as collagen I and III, tenascin-C, elastin and fibronectin [195].

It must also be noted that the fibre alignment in scaffolds is also importance to direct the fate of the cells under the cyclic loading [131,196]. For instance, hMSCs-seeded PCL aligned microfibres showed greater expressions of collagen types I and III compared to crimped and random fibres under cyclic loads [103]. Furthermore, the simultaneous application of BMP-12 growth factor and cyclic loading for hydrogel-coated electrospun scaffolds resulted in synergistic enhancement in MSCs adhesion, proliferation, differentiation, and alignment [197]. The frequency and magnitude of the force/displacement are also important to achieve effective tissue regeneration around a scaffold. Over-loading of scaffolds and tendons has been reported to lead to the inflammation of the tendon, and subsequently, loss of biomechanical properties [9,198].

Summary. Although it has been shown that use of signaling strategies is beneficial to enhance the outcome of TL regeneration, more work is required to clarify the interaction of different growth factors, cell types, and mechanical with the novel scaffolds' biopolymers. Selecting and formulating biopolymers requires enough knowledge and experience about biomaterials to tune the properties based on the biocompatibility, viscosity, biodegradation, and biomechanics. The ideal biopolymer needs to simultaneously meet several criteria, such as high level of biocompatibility with stem cells, tailored biodegradation rate for controlled release of growth factors, and ability to withstand significant cyclic loading [9]. Natural biopolymers, mainly in gel forms, could be an ideal choice to encapsulate biochemical molecules and act as a temporary extracellular matrix (ECM); however, natural hydrogels are often limited by their poor mechanical properties and fast degradation profiles. Crosslinking methods, e.g. photo-crosslinking, can tune the stiffness and release profile of growth factors to a certain extent, and gradients in stiffness and release profiles can be designed for TL interfacial tissue engineering by using a graded crosslinking degree of some hydrogels, like GelMA [199]. However, synthetic biopolymer or silk fibres are superior to natural hydrogels in terms of mechanical properties. Hence, an effective scaffold system could include a strong fibrous component, based on synthetic biopolymers, coated with a natural hydrogel containing biochemical molecules to signal stem cells. In addition, the appropriate signaling strategy may involve a heterogeneous scaffold based on multi-biopolymers with autologous stem cells stimulated with a combination of growth factors and mechanical stimulation that direct the tissue regeneration. However, further research will be required to formulate biopolymers based on specific tissue target and designed signaling strategies.

5. Biopolymers in commercial tendon and ligament grafts

Many commercial TL grafts have been developed based on natural and synthetic materials during the last 2 decades. Both natural and synthetic scaffolds can cause adverse events such as noninfectious effusion and synovitis, which result in the failure of surgery [200].

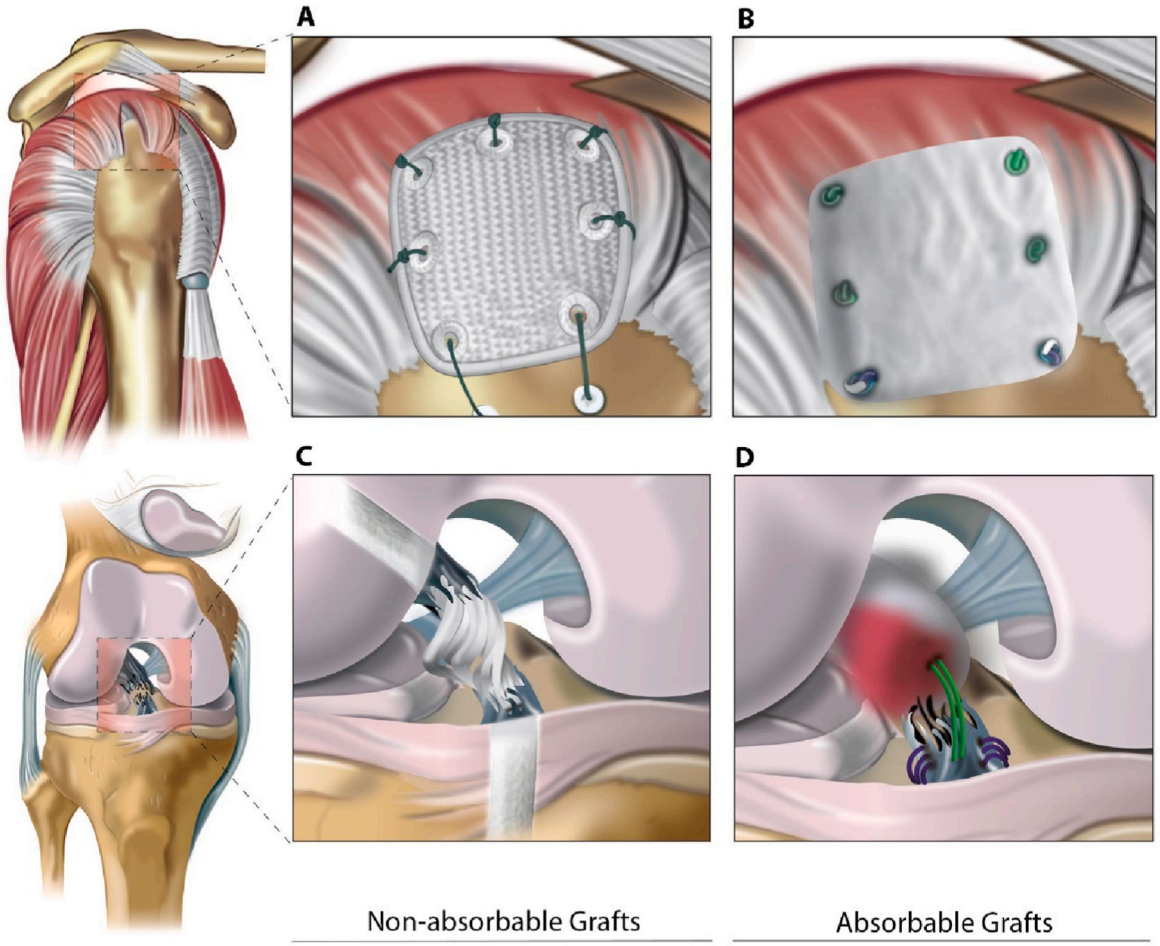


Fig. 6. Commercial TL scaffolds based on absorbable and non-absorbable biopolymers. (A) Pitch-Patch graft is designed for reinforcement of the rotator cuff as a non-absorbable graft, sutured via multiple sutures directly to rotator cuff tissue. The designed suture holes in Pitch-Patch resist suture cut-through. (B) CelGro™ for augment repair of rotator cuff tears. Torn tendon must be trimmed and anchored with sutures back into healthy bone prior placing the CelGro™. Then, CelGro™ can be trimmed to size and placed over the repair site to promote tendon healing. (C) LARS graft for ACL repair. The graft is composed of intra-articular and intra-osseous sections. The intra-articular section is based on twisted fibres; however, intra-osseous sections is based on woven fibres and fixed within osseous channels. (D) Bridge-Enhanced® ACL Repair (BEAR®) for ACL repair. The collagen scaffold is placed in the gap between the two torn sides of the ACL and saturated with the patient's blood. Two different sutures are used to cinch the saturated scaffold.

Commercial scaffolds can be categorized in both absorbable and non-absorbable grafts. Before discussing commercial graft options, some patents are reviewed to show protected the intellectual properties (IPs) of biopolymers for TL grafts application.

5.1. Patented biopolymers

Several published patents describe novel TL scaffolds based on the engineered biopolymers. To date, different preparation methods of porous collagen scaffold have been patented [201–204], since this natural biopolymer has great potential in TL tissue engineering products. The method for preparing collagen sponge scaffold for ACL repair is well protected [201,205–207] with synthetic biopolymers, like PLLA, PGA and PLGA, also covered in a patent claiming methods to fabricate three-dimensional (3D) braided scaffolds as TL replacement constructs [208].

There are also patents protecting the formulation of hybrid biopolymers for TL regeneration. For instance, a hybrid biopolymer fibre covering the compositions based on 20–35 wt% of type I collagen and 65–80 wt% of PDLLA [209]. Moreover, the method for fabricating an implantable scaffold for TL repair based on those compositions was covered in a separate patent, disclosing electrospinning of PDLA/collagen solution followed by an annealing process to enhance structural stability of the scaffold [210].

Patents describing the design, technology and composition of complex scaffold systems, including natural and synthetic components, are also published. For instance, an implantable scaffold, based on ultrahigh molecular weight polyethylene (UHMWPE) fibres, polyvinyl alcohol hydrogel and ceramic material, is patented for partial or full tendon or ligament repair applications [211]. The combination of the hydrogel and polymer fibres was considered to remodel ECM hierarchical structure of native tendons or ligaments. Another hybrid scaffold system, comprising braided polymeric fibres and porous collagen component, covers reinforcing and healing rotator cuff tendon and ACL [212]. While the braided fibres can be made of different synthetic absorbable polymers, like PLA, PGA, PLGA, and PCL, to provide mechanical support after implantation, the collagen component with inter-connected pores enables distribution and in-growth of tendon cells.

Although many patents have been published to protect intellectual property of TL scaffolds based on the engineered biopolymers, only a few of those have been successfully commercialised so far.

5.2. Non-absorbable grafts

Non-absorbable polymers have been studied as permanent reconstructions in TL repair. For instance, hierarchical Nylon 6,6

electrospun bundles showed comparable failure stress (63.5 ± 11.0 MPa) to native tendons and ligaments fascicles (6.8–28.1 MPa) [213,214]. However, polyethylene terephthalate (PET) is most popular non-absorbable synthetic biopolymer in production of commercial TL grafts such as the Ligament Augmentation and Reconstruction System (LARS) (Corin Group, UK), Poly-Tape (previously named Leeds-Keio, Neoligaments Ltd., UK), and Pitch-Patch (Neoligaments Ltd., UK).

LARS grafts are made of PET fibres through braiding, twisting and weaving textile technologies. The latest generation of LARS graft is composed of two sections: intra-articular and intra-osseous as shown in Fig. 6. Intra-articular is an active section enabling articular movement and based on twisted fibres for fatigue resistance and fibroblastic ingrowth. On the other hand, intra-osseous is a non-moving section to secure the ligament within osseous channels and based on woven fibres for high strength and resistance to elongation.

Poly-Tape meshes are manufactured by weaving the PET fibres. While the open woven structure of Poly-Tape supports space for tissue ingrowth, the parallel fibres provide high strength. Pitch-Patch (Neoligaments Ltd., UK) was particularly designed for rotator cuff tears (RCTs) repair (Fig. 6). This non-absorbable patch is constructed from polyester knitted fabric with integral eyelets, which can increase the security of suture attachment. The average tensile strength for the medium and larger patches are over 400 N and 550 N, respectively [215].

Other non-absorbable grafts, like polypropylene patch (Repol Angimesh) [216], and polycarbonate polyurethane patch (manufactured by Biomerix) [217], also indicated improvement in outcomes for the reconstruction of RCTs and ACL.

5.3. Absorbable grafts

Collagen is often considered for TL scaffolds since it is an ECM-based biomaterial with excellent bioactivity [218]. Collagen can be extracted and processed by chemical treatments to form the bioactive scaffolds in TL regeneration. CelGro™ (Orthocell Ltd.) is a porcine-derived collagen membrane, which is prepared by denaturing and removing non-collagenous proteins through several steps of chemical treatment. During preparation, the membrane is subjected to mechanical stretching to achieve the desired size and thickness, resulting in a bilayer structure composed of a smooth side of densely oriented collagen fibres, and a rough side of randomly distributed collagen fibres [219]. The average ultimate tensile strength of 0.35 ± 0.06 MPa (failure force of 5.4 ± 0.38 N) was reported for CelGro™ [219]; therefore, this scaffold is not recommended as a structural graft, but rather, is promising for induction of tendogenesis into the healing areas of tendon and tendon-bone interfaces, especially for RCTs (Fig. 5) based on clinical studies [220,221].

The Zimmer® Collagen Repair Patch (Zimmer, IN, USA), formerly known as Permacol™, is a cross-linked collagen scaffold obtained from porcine dermal tissue, which is designed for rotator cuff repair. It is mainly composed of type I collagen (93%–95%) with type III collagen and a small content of elastin [200]. After pre-treatments, organic and enzymatic extractions are performed to remove cellular materials, soluble proteins, and fats. The collagen is then chemically crosslinked by hexamethylene diisocyanate [222]. It was reported that the surgical augmentation using Zimmer Patch can reduce pain, resulting in higher patient satisfaction and better functionality in comparison to non-augmented repairs [223]. The scaffold has proven to be good in cell infiltration and rapid revascularization. In tensile tests, the average maximum load and tensile strength of the Zimmer patch are approximately 175 N and 12 MPa, respectively [224].

GRAFTJACKET NOW™ (Wright Medical Group, Inc.) is sourced from cadaver human skin, which undergoes processing to remove the cellular component while preserving the native protein, collagen structure, blood vessel channels, and essential biochemical composition [200]. As it is rendered acellular during processing, it lacks many of the disadvantages typical of standard allograft tissue. The resulting patch is an acellular tissue, made of collagen types I, III, IV, VII, elastin, chondroitin sulphate, proteoglycans, and fibroblast growth factor [225]. Satisfactory results have been described using GRAFTJACKET to repair Achilles tendons [226,227], rotator cuff [228], patellar tendon [229], and quadriceps tendon [230]. GRAFTJACKET is highly biocompatible, enables revascularization, and has strong biomechanical functionality with mean load to failure of 229 N [231]. However, the mean load-to-failure strength of the supraspinatus tendon augmented with GRAFTJACKET was 325 ± 74 N, which was higher than the strength of the control construct (273 ± 116 N) [222].

TissueMend (developed and manufactured by TEI Biosciences, USA, and distributed by Stryker Orthopedics, USA) is a single layer collagen base scaffold derived from fetal bovine dermis. The material is produced using a series of procedures to remove cells, lipids, and carbohydrates, and then sterilized in ethylene oxide. The product is 99% non-denatured fetal bovine collagen, which is not artificially cross-linked [222]. TissueMend demonstrated the mean load to failure of 76 N [200,231] and could be used to repair rotator cuff, patellar, Achilles, biceps, quadriceps or other tendons [232]. At the time of implantation, the highly porous material readily traps blood, acting as a sponge to trap cells, growth factors, and cytokines, to seed the matrix. The biomaterial is rapidly repopulated with host cells and supporting vasculature [233].

Bridge-Enhanced® ACL Repair (BEAR®) is technique based on a collagen scaffold for ACL repair. The collagen scaffold originates from bovine tissue and is formed into a solid porous cylinder after chemical and physical treatments [234,235]. The collagen scaffold is then placed in the gap between the two torn sides of the ACL and saturated with the patient's blood (Fig. 6). Non-absorbable and absorbable sutures are used to cinch the saturated scaffold through a specific suturing technique [236]. The primary results of 2-year follow-up clinical trials for BEAR® were comparable with the results of the current gold standard of ACL reconstruction with autograft, resulting in FDA Marketing Approval of the first implant labelled for use in augmenting ACL healing. However, further studies are recommended to optimize the surgical technique and improve in outcomes [237,238].

X-Repair (Synthasome, USA) is an absorbable surgical mesh made of PLLA and can be sutured over torn tendon tissue as reinforcement. This mesh has high tensile strength (2500 N, for 2.5 cm wide device) and high suture retention strength (550 N, for 2.5 cm wide device) which allows it to be sutured in situ and used to reinforce surgical repair of TL tissue such as rotator cuff, patellar, Achilles, biceps and quadriceps tendons. X-repair mesh degrades slowly and retains more than 90% of its mechanical properties over one year [239].

Artelon produces different knitted/braided grafts, like Dynamic Matrix™ and FLEXBAND™, based on the co-polymer of PCL and poly (urethane urea), which is known as a slow absorbing (or partially absorbable) material. The grafts degrade by hydrolysis up to 6 years, which results in to resorbable and a non-resorbable fractions; however, they retain 50% of the initial strength after 4 years [240].

Other synthetic absorbable grafts were also employed for TL tissue repair. For example, Neoveil sheet (GUNZE Ltd., Japan), made from PGA, was clinically tested for healing RCTs without any serious complication [241]. Neoveil sheet is a soft non-woven fabric which is absorbed for about 15 weeks due to fast hydrolytic degradation of PGA. Hence, it is recommended for applications that do not require long-term reinforcement [242]. The information of absorbable and non-absorbable commercial graft are listed in Table 3.

Table 3
Properties and information of absorbable and non-absorbable commercial graft for tendon and ligament repair.

Type of graft	Product name	Manufacturer/ distributor	Material type	Tissue Source	Repair target	Mechanical properties	Other properties
Absorbable	Zimmer Collagen Repair Patch [224,243]	Zimmer	Collagen and elastin	Porcine dermal tissue	Rotator cuff	Max load to failure: ~ 175 N Max tensile strength: ~ 12 MPa	Thickness of 1.5 mm; Random porous structure; Chemically crosslinked; Resistant to enzymatic degradation
	GRAFTJACKET NOW [225,227]	Wright Medical Group, Inc.	Collagen, elastin, growth factors	Cadaver human skin	Rotator cuff, Achilles tendon, patellar tendon, quadriceps tendon	Max load to failure: ~ 229 N	Random porous structure
	Tissuemend [200,231]	TEI Biosciences	Collagen	Fetal bovine dermis	Rotator cuff, patellar, Achilles, biceps, quadriceps or other tendons	Max load to failure: ~ 76 N	
	CelGro™[219,221]	Orthocell	Collagen	Porcine or bovine tissue	Rotator cuff and its BTJ	Max load to failure: ~ 5.4 N	Bilayer structure consisting of a rough and smooth side; Random porous structure
	Bridge-Enhanced® ACL Repair (BEAR®) collagen scaffold [234, 235]	BEAR group, Boston Children's Hospital	Collagen	Bovine tissue	ACL and its BLJ	Not reported	Cylindrical shape; Solid porous structure
	X-Repair [239]	Synthasome	PLLA	Not applied	Rotator cuff, patellar, Achilles, biceps and quadriceps tendons	Max load to failure: ~ 2500 N Max suture retention load: ~ 550 N	Woven mesh with regular pore sizes; Manufactured in a variety of sizes
	FLEXBAND™[244,245]	Artelon	Polycaprolactone based-polyurethane urea (PUUR)	–	ACL, Rotator cuff, biceps tendon	Max load to failure: ~ 172 N (0.5 mm FLEXBAND™)	Partially absorbable knitted graft
Non-absorbable	LARS [200]	Corin Group	PET	–	ACL	Max load to failure: ~ 998 N	Based on braiding and weaving; Intra-articular-twisted fibres for fatigue resistance; Extra-articular-woven fibres for high strength
	Poly-Tape [215]	Neoligaments	PET	–	ACL, quadriceps tendon, patellar tendon	Max load to failure: ~ 1200 N (for JwelACL)	Open weave structure; Parallel fibres provide high strength
	Pitch-patch [215]	Neoligaments	PET	–	Rotator cuff	Max load to failure: ~ 450–550 N	Knitted fabric with reinforced suture holes to resist suture cut-through

6. Conclusion, challenges and future directions

Many studies have shown the potential of the novel developed biopolymers, integrated with scaffold architecture or signaling strategies, for regeneration of TL and enthesis. However, only a few of those have been commercialised or reached the clinical trials so far, due to the inadequacy of mechanical properties, degradation rate, and biological response.

Biopolymers, both natural and synthetic, have been reviewed for regeneration of TL and their interfaces. On one hand, mechanical properties, uniformity of microstructure, controlled degradation rate and easy reproducibility with large-scale production are key advantages of synthetic biopolymers. On the other hand, natural biopolymers show a high degree of scaffold–tissue compatibility due to the positive biological recognition of their chemical make-up. The excellent chemical conjunction between the functional groups in natural biopolymers with other biomolecules, such as growth factors, allows controlling the gradient differentiation of stem cells in TL interface scaffolds. But despite these advantages, natural biopolymers generally have relatively weak tensile properties and show low processability when compared to synthetic ones, which restrict their application to remodel the mechanical properties of TL tissues.

The combination of natural and synthetic biopolymers can overcome many limitations of each group, particularly once a scaffold system is required to mimic complex tissues like tendon/ligament-bone junctions. PLA/collagen and PCL/gelatine blends are good examples of hybrids biopolymers for tendon tissue engineering, that can be further enhanced through the addition of mineral particles to mimic the biocomposition of native bone-tendon/ligament junctions.

Ideal biopolymers for TL repair and regeneration need to possess the appropriate biological and biomechanical properties necessary for the successful repair and regeneration of ruptured TL tissue. Hence, advanced biocomposites need to be developed based on the properties of the human native tissue to achieve better outcomes for pre-clinical studies; however, limited studies have been conducted to characterise the structural, biomechanical, and biocompositional properties of different TL tissue. In particular, the complex heterogeneous structural and cellular composition of the native interface makes the TL interface tissue engineering challenging. For instance, the mechanical response of the tendon-bone interface region is highly heterogeneous in the lateral direction and also angle-dependent, which requires precise micromechanical tests on enthesis while simultaneously acquiring high-resolution images to measure the gradient of mechanical response [246]. Although the mechanical properties of scaffolds depend on the biopolymer selection, scaffold architecture can influence final mechanical performance. On one hand, fabrication techniques govern architectural properties by their accuracy and capabilities. On the other hand, fabrication techniques restrict the development of novel biopolymers for TL tissue engineering. For instance, melt-electrowriting (MEW) enables the development of complex architectures by predefining a single small diameter fibre deposition with high accuracy and stability; however, this technique is typically limited to PCL due to the low operation temperature and rapid solidification of the material [159]. Hence, fabrication of MEW scaffolds for TL tissue engineering based on novel hybrid biopolymers is challenging. Thus, electrospinning offers advantages over MEW as it is compatible with a wide range of biopolymers and composites.

Another challenge in the development of biopolymers is the interaction between the biomaterial, cell types, growth factors and mechanical stimulation. For example, the optimal stimulation of MSCs when interacting with growth factors and mechanical loading is influenced by the formulation of hydrogels to generate a functional heterogeneous TL enthesis construct. Despite the remarkable work on complex scaffold system based on novel biopolymers, there is great difference in complexity between scaffold performance during *in vivo* and *in vitro* studies of commercially available scaffolds. This highlights an important challenge when considering the technology translation of a complex biomimetic scaffold as many rely on non-FDA approved biomaterials integrated with therapeutic agents. As a result, most of the current commercial tendon scaffolds are based on either natural or synthetic biopolymers. Although the synthetic tendon grafts made of PET have been widely used over the past decade, they are non-absorbable, so the tissue cannot be truly regenerated with its structural and compositional complexity. Collagen has been recently used in commercial tendon scaffolds, and despite their limited mechanical strength, they are currently a popular option for TL regenerative biomaterial-based treatment.

In the future, the long-term outcomes on large animal models are essential to evaluate the complete biofunctionality of the advanced scaffolds to confirm that the generated tissue is identical with the properties of the native tissues. The combination of collagen with FDA approved synthetic biopolymers should be considered for commercial TL grafts to provide better mechanical properties along with biocompatibility. Furthermore, the properties of novel biopolymers must be engineered to suit several criteria, including the complexity of native TL and bone-TL interface tissue, the biofabrication technologies and integration of therapeutic agents. This is not only technically challenging but also requires consideration of regulatory approval pathways, as functional and advanced biomaterials represent complex approval processes for device manufacturers.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Minghao Zheng is consultant to Orthocell Ltd and hold stock in the company.

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Appendix A. Supplementary data

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