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Application and optimization of bioengineering strategies in facilitating tendon–bone healing

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Abstract

Tendon–bone insertion trauma is prevalent in both rotator cuff and anterior cruciate ligament injuries, which are frequently encountered conditions in the field of sports medicine. The main treatment for such injuries is reconstructive surgery. The primary determinant impacting this process is the graft's capacity to integrate with the bone tunnel. In recent years, researchers have attempted to use a variety of methods to facilitate tendon–bone healing after reconstructive surgery. Such as the implantation of biological materials, cytokines and the local application of permanently differentiated cells from various sources. However, there are limitations to the efficacy of one therapy alone in facilitating tendon–bone healing. Therefore, researchers are trying to combine strategies to overcome this conundrum. At present, most studies are based on biomaterial combined with other therapeutic strategies for tissue repair and regeneration. Biomaterials mainly include the application of bioengineering scaffolds, hydrogels and bioabsorbable interference screws. By conducting a thorough review of relevant literature, this study provides a comprehensive overview of the present research progress in enhancing tendon–bone healing using biomaterials. Additionally, it explores the potential benefits of combining biomaterials with other approaches to promote tendon–bone healing. The ultimate goal is to offer insights for future basic research endeavors and establish a solid groundwork for advancing clinical applications in the near future.

Keywords: Tendon–bone insertion, Tendon–bone healing, Tissue-engineered scaffolds, Hydrogel, Bioabsorbable interference screw, Enthesopathy

Introduction

With the increasing emphasis on encouraging the general population towards regular physical activity, the incidence of tendon–bone insertion (TBI) injuries has increased [1]. The main cause is tendinopathy during exercise, a clinical condition caused by overuse of the tendons. Tendon degeneration is considered to be a risk factor for acute tendon rupture [2–4]. TBI injuries are common in the workplace as well as in sports, such as rotator cuff (RC) and anterior cruciate ligament (ACL) injuries [5]. To treat this

orthopedic injury, the damaged tendon or ligament is repaired by transplanting it into a bone tunnel, thereby restoring its connection to the bone tissue [6, 7]. Reconstructive surgeries depend on the graft's ability to fuse with bone for success. Despite reconstruction, the biochemical and mechanical properties of healed tendon tissue may never be comparable to those of intact tendons [8]. The natural ability of adult tendons to heal is limited, and current treatments frequently prioritize surgery, which often yields unsatisfactory outcomes [9]. This fusion of graft with bone is known as tendon–bone healing [10]. The result of tendon–bone healing directly affects the efficacy of tendon reconstruction surgery. According to studies, RC repair has a failure rate of 20–94% [11], while ACL reconstruction has a failure rate of 10–25% [12, 13]. The main reason for the above situation is the formation of scar tissue in the process of tendon–bone healing, and its poor mechanical properties can easily lead to reinjury of the healing interface [12]. Furthermore, poor tendon–bone healing can lead to secondary symptoms involving knee joint, including joint instability, cartilage damage, and post-traumatic osteoarthritis [14, 15]. The site of bone tunnel fusion is the weakest part of postoperative healing. To prevent overloading of the transplanted tendon, delaying exercise and physical therapy is crucial [16–18]. Therefore, the above results in a long postoperative recovery period for patients, unable to resume exercise as soon as possible.

In the clinical practice of sports medicine, tendon–bone healing mainly involves two kinds of tissue fusion with different properties and densities, and is also considered to be the pivotal factor for the success of many injured tendon reconstruction surgeries [19]. At present, effective fusion of the tendon–bone interface remains challenging. It has been shown in studies that effective strategies to facilitate tendon–bone healing can reduce patients' risk of secondary injury and allow them to return to work and exercise earlier [20]. The aim of many researchers is therefore to develop effective strategies for facilitating tendon–bone healing. Angiogenesis and osteogenesis are two physiological processes involved in tendon–bone healing [21]. Therefore, it is possible that measures that are beneficial to angiogenesis and osteogenesis may be used to facilitate tendon–bone healing. Over the past decade, researchers have developed a number of biological strategies to facilitate tendon–bone healing. It mainly includes growth factors [22], platelet-rich plasma (PRP) [23], permanently differentiated cells from different tissue sources [24, 25], gene modified stem cell technology [26], biological materials [27, 28] and other technologies [29, 30]. The above strategies have been proved to facilitate tendon–bone healing in preclinical studies [31–35], and some of them have been used in clinical studies [36]. Several preliminary studies have demonstrated that these strategies are effective in facilitating tendon–bone healing.

However, studies have shown limitations in the effectiveness of these strategies alone in facilitating tendon–bone healing [37, 38]. Therefore, researchers are trying to combine strategies to overcome this conundrum. At present, most studies are based on biomaterial combined with other therapeutic strategies for tissue repair and regeneration [39–43]. Biomaterials mainly include the application of bioengineering scaffolds, hydrogels and bioabsorbable interference screws. Previous studies have shown that these biomaterials in combination with other strategies can significantly enhance the function of promoting tendon–bone healing [36, 44, 45]. This paper comprehensively summarized the current research status on the application of biomaterials to facilitate tendon–bone

healing and the optimization of strategies by searching related literature. Finally, the value and challenges of biomaterials in this area are discussed. Through this review, sports medicine clinicians can quickly understand the research progress in this field, and provide the direction for the next research or the selection of clinical treatment.

Pathological process

Tendon–bone healing is currently thought to be mediated by the formation of fibrous vascular interfaces, and the subsequent gradual growth of bone tissue into the interface [46]. After the operation, collagen fibers in the bone canal were wound with the graft and fused with the bone tunnel [47]. The mechanism of tendon–bone healing has been investigated in animal models [48]. Inflammatory cells were found at the tendon–bone interface 1 week after surgery. After 2 weeks, scar tissue appeared, and after 4 weeks, scar tissue at the tendon–bone interface gradually reorganized to form a dense connective tissue matrix, and bone and tendon fused continuously. Following a period of 6 weeks, an irregular recombination of collagen fibers and the presence of Sharpey's fibers were noted. The healed tendon–bone interface consists of four consecutive layers: bone material, calcified fibrocartilage, uncalcified fibrocartilage, and tendon material [49, 50]. Normal movement of the joint after surgery requires strong support from this transition from soft tissue to hard tissue.

ACL injury seriously damages the stability of knee joint, easily causes the damage of articular cartilage, and accelerates the progression of osteoarthritis [51, 52]. The restoration of knee function is widely considered to be highly effective through ACL reconstruction. The main cause of reconstruction failure is poor tendon–bone union. After undergoing ACL reconstruction, individuals who have achieved satisfactory healing outcomes may go through four phases, namely inflammation, hyperplasia, reconstruction, and maturation [21]. Immediately following surgery, the removal of tissue fragment and the beginning of healing can cause an inflammatory response around the transplanted tendon. Later, the pro-inflammatory cytokines facilitate cell migration and proliferation and contribute to vascular reconstruction, resulting in the formation of fibrochondrocytes within a few days of reconstruction [53]. Calcified fibrocartilage occurs at the fibrous interface several weeks after surgery. Finally, collagen fibers and bone cells gradually return to normal at the bone tunnel through the ligamentation stage, which indicates that the biological function of the knee joint has been restored.

The shoulder cuff muscle tissue provides stability to the shoulder joint by providing balanced force. This loss of intrinsic stability results in abnormal joint motion because the humeral head loses a stable pivot in the glenoid for rotation [54]. This force varies depending on the size and location of the tear. Anterior tears at supraspinatus impositions are more likely symptomatic and progression of an increased pattern of regional strain due to joint force imbalance, requiring surgical intervention [55]. However, complete RC repair after chronic multi-tendon tears may be challenging due to tendon contraction and hardening. Rotator cuff tendon healing also includes four stages: inflammation, fibroblast proliferation, reconstruction and maturation [56]. The interaction between cells and tissue growth factors during these stages ultimately results in tendon–bone healing. Despite advances in surgical techniques, healed tendons do not fully

return to their original state, often forming a three-layer fibrous vascular structure with less fibrocartilage than normal.

Poor tendon–bone interface healing can be caused by various factors, such as the formation of fibrous scar tissue, severe tendon injury, or rupture of the transplanted tendon, leading to reduced mechanical stress at the tendon–bone interface [57, 58]. This can result in joint secondary damage due to poor resistance to external mechanical forces.

During tendon–bone healing, inflammatory factors like IL-1 and IL-6 are released, followed by platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) to support angiogenesis [59, 60]. Subsequent migration of endothelial cells to the tendon–bone interface promotes the formation of new blood vessels during proliferation. At the same time, mesenchymal stem cells (MSCs) were recruited for tissue regeneration at the TBI site. During the remodeling stage, in the presence of fibroblast growth factor (FGF), transforming growth factor-β (TGF-β), and bone morphogenetic protein-2(BMP-2), cell–cell interactions trigger the formation of fibrocartilage, leading to biological integration of the tendon graft with the surface of the bone tunnel [20, 61]. The strength of tendon–bone healing is further enhanced when calcified fibrochondral interfaces are formed. During the mature stage of healing, the bone grows into the tendon–bone interface, indicating that the tendon graft is firmly attached to the surface of the bone tunnel.

To improve tendon–bone healing, strategies such as VEGF and PDGF have been used to induce blood vessel formation at the tendon–bone interface [20, 62–64]. Osteogenic cytokines including BMP, basic fibroblast growth factor(bFGF) and TGF-β are also used to facilitate tendon–bone healing due to their properties of promoting osteogenic differentiation of stem cells [31, 65, 66]. Researchers have also used biological materials as drug carriers to optimize drug release and promote bone growth through effective vectors, significantly improving tendon–bone healing quality.

The application of biomaterials to facilitate tendon–bone healing

Biomaterial scaffolds

Since biomaterial technology has developed rapidly, scaffolds made from biomaterials have been widely used in tendon and ligament repair [67, 68]. At present, the most widely used techniques are regeneration techniques based on electrospinning and self-recombination structural processes, which are, respectively, applied to tendon–bone regeneration [69]. The main polymer materials used are silk protein, polycaprolactone (PCL), polyethylene terephthalate (PET), polylactic acid (PLA), poly(lactide-co-glycolide) (PLGA). The researchers used different manufacturing processes to make these materials into biological scaffolds or nanofiber membranes for tissue repair and drug delivery [70–73]. Fiber scaffolds and fiber membranes are used to repair tendons and ligaments by different implantation methods. In addition, the researchers attempted to load the scaffolds and membranes with bone components or different cytokines to enhance their role in facilitating tendon–bone healing (Fig. 1). The above strategies have been demonstrated their potential to facilitate tendon–bone healing in animal models (Table 1). In order to promote the widespread clinical application of the above strategies,

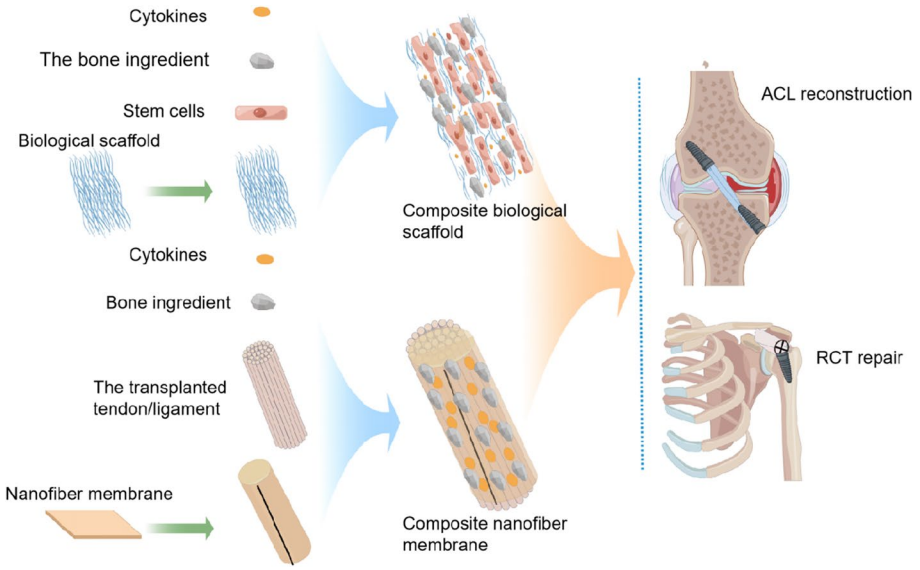

Fig. 1 Classification and construction process of composite tissue engineering scaffolds. Tissue engineering scaffolds mainly include biological scaffolds or nanofiber membranes. Biological scaffolds or nanofiber membranes are loaded with osteogenic factor or bone factor, etc., to facilitate tendon–bone healing. This figure was created by Figdraw

more basic and clinical studies are needed to explore their mechanisms of action and clinical efficacy.

Silk–collagen scaffold have been extensively studied for their excellent properties of facilitating tendon–bone healing. F. Bi et al. [74] combined the knitted silk–collagen network with type I collagen to simulate the components of ligaments to prepare the sericinogen scaffold. The rabbit model of ACL reconstruction utilized sericin scaffolds as a substitute for the ACL in this research. Over time, there was a gradual increase in the penetration of cells into the scaffold, and after 4 months of surgery, a significant population of cells resembling fibroblasts was observed within the central region of the graft. Tendon–bone healing was better in the scaffold group than in the autologous graft group, with a large number of bone trabecula growing in the scaffold. Besides, Cai J et al. [75] prepared a double-layer randomly arranged silk fibroin fiber poly (L-lactic acid-co-e-caprolactone) nanofibrous scaffold by electrospinning method, and evaluated the effect of the scaffold on tendon–bone healing in vivo. A rabbit autologous extraarticular tendon–bone healing model was used in this study. According to the results, double-layer fiber scaffolds could effectively enhance tendon–bone fusion and improve gradient microstructures by inducing new bone formation, increasing the area of fibrocartilage, promoting collagen tissue and maturation and other ways. In these studies, tissue engineering scaffolds were shown to have great potential for supporting tendon–bone healing in the clinic, and their functions can be improved by optimizing their structure.

Earlier research has indicated that the framework composed of a solitary substance is incapable of attaining full integration of self-donor graft and bone passage [76, 77]. To resolve this issue, P. Zhang et al. [78] prepared a new multifunctional fiber scaffold by layer-by-layer self-assembly method for the first time. In this study, PCL nanofiber membrane loaded with bone morphogenetic protein 7 was prepared as the degradable

Table 1 The application of tissue engineering scaffolds to facilitate tendon–bone healing

Intervening measure	Method of delivery	Treatment outcomes	Animal model	References
bFGF-loaded electrospun PLGA fibrous membrane	Local administration	It facilitates cell attachment and proliferation, accelerating tendon–bone regeneration	Rat rotator cuff repair model	Zhao S et al. [82]
PCL/nanoHA/collagen nanofiber membrane	Wrapping graft tendon	PCL/nanoHA/collagen nanofiber membrane can effectively facilitate the healing of tendon and host bone	Rabbit ACL reconstruction	Han F et al. [81]
Silk–collagen scaffold	Replace the anterior cruciate ligament	This scaffold can induce the trabecular bone to grow within the scaffold and facilitate tendon–bone healing	Rabbit ACL reconstruction	F. Bi et al. [74]
Biodegradable PLA bolt and PLGA nanofibrous membrane	Local implanting	The composite polymer of PLA bolt and PLGA/ collagen nanofiber membrane can effectively facilitate rabbit tendon reconstruction, reduce tunnel enlargement	Rabbit ACL reconstruction	Chou Y C et al. [84]
SF mat	Wrapping graft tendon	SF mat can facilitate tendon–bone healing in soft tissue graft	Rabbit ACL reconstruction	Zhi Y et al. [43]
Silk fibroin/poly (L-lactic acid-co-e-caprolactone) nanofibrous scaffold	Wrapping graft tendon	This nanofiber scaffold has good cytobiocompatibility and can effectively facilitate tendon–bone healing, which provides a new method for the clinical application of modified grafts to reconstruct ACL	Rabbit ACL reconstruction	J. Cai et al. [79]
Dual-layer aligned-random scaffold (ARS)	Local implanting	ARS can significantly improve the gradient microstructure by inducing new bone formation, increasing the area of fibrocartilage and promoting the maturation of collagen tissue	Rabbit Achilles tendon repair model	Cai J et al. [75]
Silk fiber-based ACL scaffold	Replace the ACL	This collagen-fibrous scaffold continuity is partially composed of Sharpey fibers and is comparable to known tendon–bone healing with autograft and allograft	Sheep ACL reconstruction	A. H. Teuschl et al. [80]

Table 1 (continued)

Intervening measure	Method of delivery	Treatment outcomes	Animal model	References
PCL fibrous membranes loaded with KGN	Wrapping graft tendon	KGN-PCL membrane can significantly facilitate chondrogenic and tendinogenic differentiation of rat bone marrow stromal cells	Rat rotator cuff repair model	Q. Zhu et al. [83]
Hybrid biomimetic artificial ligament scaffold	Replace the anterior cruciate ligament	This scaffold significantly facilitates the fusion of the hybrid ligament with the bone tunnel, thus achieving true "ligamentization" after ACL reconstruction	Rabbit ACL reconstruction	P. Zhang et al. [78]
Silk–collagen scaffold modified by HA	Local implanting	The scaffold can facilitate bone fusion at the tendon–bone interface	Rabbit ACL reconstruction	Bi F et al. [44]
HA incorporated PLA aligned nanofibrous membranes	Wrapping graft tendon	PLA-HA nanofiber membrane can increase the expression of alkaline phosphatase in BMSCs	Rat rotator cuff repair model	Lv Y et al. [28]
Natural fish scale (FS) modified by calcium silicate nanoparticles (CN)	Local fixation	In vivo, CN-FS facilitates the repair of transitional tissue between tendon–bone, and exerts an active integration role in promoting the repair of bone–tendon interface	Rat and rabbit rotator cuff repair model	Han F et al. [27]

part of the composite scaffold, and then the degradable part and PET mesh fabric (non-degradable part) were rolled into a composite scaffold structure. According to the findings, this fiber framework has the potential to greatly improve the compatibility with living tissue of pure PET ligaments, thereby aiding in cell mineralization and promoting the fusion of combined ligament and bone tunnel. Similarly, Bi F et al. [44] explored the effect of sericinogen scaffolds modified with hydroxyapatite (HA) at both ends on bone integration and prevention of osteoarthritis at the tendon–bone interface. In the preparation of the HA/silk–collagen scaffold, a degummed knitted silk–collagen scaffold was used, as well as a type I collagen matrix and simulated body fluids. As grafts, rolled up HA/sericinogen scaffolds were used to replace the original ACL, while sericinogen scaffolds served as controls. It was found that the HA/sericinogen scaffold increased the mass of mature bone and the deposition of type I collagen and osteocalcin at the tendon–bone interface. The application of HA/sericinogen scaffolds can better prevent osteoarthritis and further promote bone fusion at the tendon–bone interface. Based on these studies, tissue-engineered scaffolds infused with bone growth factors or bone components can facilitate tendon–bone healing. Furthermore, fibrous scaffolds incorporating various materials and structures are also being investigated as a way to improve tendon–bone healing.

It is also being investigated whether inoculating cells or blood components into tissue-engineered scaffolds can enhance their ability to facilitate tendon–bone healing. J Cai et al. [79] prepared silk fibroin/poly (L-lactic acid-co-e-caprolactone) nanofiber scaffold by electrospinning. Preosteoblast MC3T3-E1 cells were inoculated on this scaffold, and then the scaffold was used to wrap autogenous tendon transplantation in rabbit ACL reconstruction model. As a result of implanting MC3T3-E1 cells in the scaffold, they grew well and showed obvious proliferation effects. The tendon–bone interface was infiltrated with inflammatory cells 6 weeks after surgery. There was a significant increase in new bone formation, failure load, and stiffness at the tendon–bone interface 12 weeks after surgery compared with the control group. Similarly, A.H. Teuschl et al. [80] designed a filament ACL scaffold and tested its ability to initiate osseointegration during in vivo use. The study involved implantation of autologous tissue fluid (an adipose-derived stem cell-rich isolate) into the scaffold in order to enhance osseointegration. However, it was not found histologically to enhance bone integration. Although the above studies have produced different results, inoculating nanofiber scaffolds with cells beneficial to tendon–bone healing is still a strategy for optimizing tissue engineering scaffolds. More studies are needed to verify its efficacy by inoculating different types of cells and tissue fluid components.

In addition, researchers are attempting to fabricate tissue-engineered scaffolds into membranes that can be wrapped around autografted tendons or ligaments for repair and reconstruction. Zhi Y et al. [43] firstly prepared electrospinning silk fibroin (SF) into electrospinning SF pad and applied it to facilitate tendon–bone healing. The results of this study showed that rabbit BMSCs proliferated well on electrospinning SF pads. The electrospinning SF pad wrapped with autogenous Achilles tendon was transplanted into the bone tunnel of the rabbit model outside the joint. The electrospinning SF pad can facilitate the healing of the tendon–bone. The above studies indicate that the membrane structure prepared by tissue engineering scaffolds to wrap autogenous tendons can effectively facilitate the healing of tendon and host bone in ACL reconstruction.

Over the past few years, the use of nanofiber membranes loaded with cytokines and bone components has also been investigated to stimulate tendon–bone healing. Han F et al. [81] explored a bionic PCL/nano-HA/collagen nanofiber membrane (PCL/nHAp/Col). The effect of the nanofiber membrane on tendon–bone healing was examined by the rabbit ACL reconstruction model. Tendons wrapped in PCL/nHAp/col nanofiber membrane may have better tissue integration and better mechanical strength than unwrapped tendons, according to in vivo studies. Likewise, Lv Y et al. [28] prepared a nanofiber membrane combined with HA and PLA by electrospinning, and tested its role in facilitating tendon–bone healing. The results showed that PLA-HA nanofiber membrane can increase the expression of alkaline phosphatase in rat BMSCs, indicating that electrospun PLA-HA nanofiber membrane can better induce bone formation of rat BMSCs. In addition, Zhao S et al. [82] reported an electrospun PLGA membrane loaded with bFGF for rotator cuff tear (RCT) repair. In this study, implantable biodegradable bFGF-PLGA fiber membrane was successfully prepared by emulsification electrospinning technology, and its efficacy in chronic RCT repair in rats was evaluated through in vitro and in vivo experiments. The results of this study showed that electrospinning fiber membrane facilitated tendon–bone reconstruction by increasing cell attachment

and proliferation, and PLGA fiber membrane loaded with bFGF had a better effect on tendon–bone healing. Kartogenin (KGN) is a powerful inducer of multipotent MSCs to differentiate into chondrocytes, effectively inducing MSCs to differentiate into chondrocytes. Q. Zhu et al. [83] prepared PCL fiber membrane loaded with KGN nanofibers by electrospinning, and studied the release of KGN from PCL membrane and its effect on the differentiation of MSCs. Results showed that PCL membranes loaded with KGN significantly promoted differentiation of rat bone marrow stromal cells into chondrogenic and tendinogenic lines. In addition, it was also found that the application of KGN-PCL membrane in acute rat RCT model promoted the formation of fibrocartilage and collagen tissue, and increased load failure. The above studies confirmed that the nanofiber membrane loaded with bone components and cytokines may be an ideal strategy to facilitate tendon–bone healing.

Biomaterials with high strength and high biological activity are also important in facilitating tendon–bone healing. Recently, Han F et al. [27] used natural fish scales (FS) modified with calcium silicate nanoparticles (CN) as a new biomaterial (CN-FS) to try to facilitate tendon–bone healing. The scaffold benefits from its "Bouligand" microstructure and maintains good tensile strength and toughness, which well meets the requirements of tendon repair. Besides, CN-FS has demonstrated diverse biological activity by stimulating the differentiation and phenotypic maintenance of multiple cell types involved in the composition of tendon–bone junctions, such as BMSCs, chondrocytes, and tendon stem/progenitor cells. In animal models of RCT, CN-FS regulates tendon–bone interface regeneration and biomechanical function through activation of the BMP-2/Smad/Runx2 pathway. The excellent strength and bioactivity of natural biomaterials make them ideal materials for supporting tendon–bone healing.

Hydrogel

Hydrogel is a kind of three-dimensional network scaffold material formed by high hydrophilic molecules crosslinking, which has the characteristics of controllable physical and chemical properties and good biocompatibility [84]. In recent years, the technical progress of hydrogel preparation process has pushed it to clinical application, and people began to pay great attention to its value in the treatment of tendon–bone healing [85]. The diameter of hydrogel can be adjusted in the micron range, resulting in improved loading rate and encapsulation efficiency, extending the retention time of drugs or cytokines in the joint [45]. As mentioned above, the tendon–bone healing process consists of two major physiological processes, angiogenesis and osteogenesis. There is evidence from previous studies that that permanently differentiated cells, cytokines and other drugs can facilitate tendon–bone healing through the above process. However, it is difficult to achieve sustained and effective drug release by applying drugs to the joint. Therefore, the development of a single compartment system combining cytokines, drugs and stem cells in a multifunctional hydrogel may solve this problem. Over the past few years, a number of studies have explored the value of using hydrogels alone or using hydrogels loaded with cytokines, permanently differentiated cells, and other chemical agents in facilitating tendon–bone healing (Fig. 2). There has been evidence that a hydrogel injection strategy can speed up the

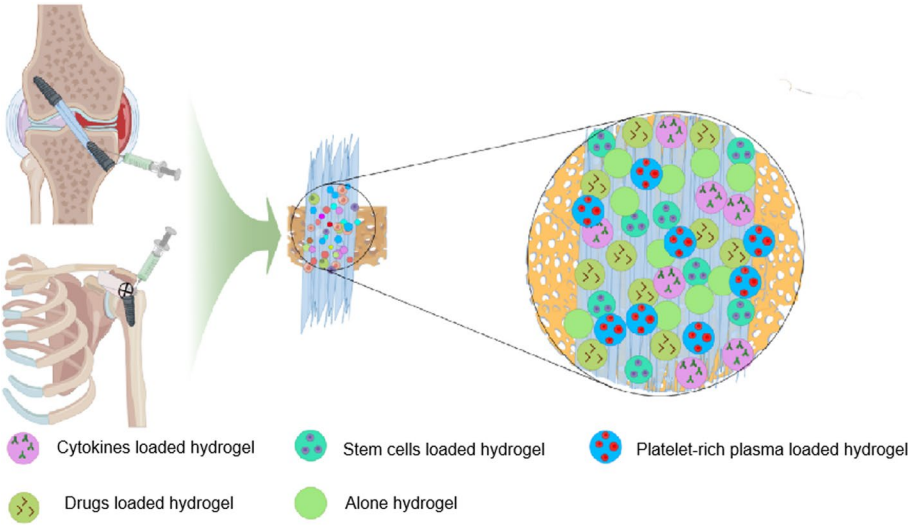

Fig. 2 The strategies of applying hydrogels to facilitate tendon–bone healing. It mainly includes cytokines loaded hydrogel, stem cells loaded hydrogel, platelet-rich plasma loaded hydrogel, drugs loaded hydrogel and alone hydrogel. This figure was created by Figdraw

healing process of the tendon–bone interface, accelerate the proliferation and differentiation of cells, further facilitate tendon–bone healing and restore joint function (Table 2).

It was found that tendon-derived hydrogel (tHG) can prominently improve tendon healing in animal models [86], and further studies have found that the potential mechanism by which tHG improves healing is through attracting homing of stem cells throughout the body [87, 88]. A. Franklin et al. [88] evaluated the homing effect of tHG on systemic adipose-derived stem cells (ADSCs) using acute and chronic tendon injury models. The injured site was treated with normal saline or tHG, and one week after treatment was given caudal intravenous injection ADSCs. Finally, flow cytometry confirmed the induced chemotaxis of ADSCs in the injured site treated with tHG. This study demonstrated that tHG can induce ADSCs to migrate to the site of tendon injury and facilitate tendon–bone healing. This may be one of the mechanisms that tHG improves tendon repair and TBI healing.

At present, failure of RC repair often occurs due to poor tendon–bone interface healing. As a means of resolving this difficult situation, C. H. Chen et al. [89] devised an injectable hydrogel made from periosteum progenitor cells (PPCs), polyethylene glycol bisacrylic acid combined and BMP-2 for tendon–bone healing in RC repair. In this study, injectable PPCs-BMP-2-hydrogel was applied to the tendon–bone interface through bone tunnel for tissue repair. Results suggest that cells and cytokines can be encapsulated and delivered locally to the tendon–bone interface by injection and photopolymerization, and they can facilitate healing of tendon–bone connection by inducing fibrocartilage regeneration. Besides, K. W. Lee et al. [90] studied the efficacy of injectable collagen gel loaded with BMP-2 to facilitate tendon–bone healing. In this study, a rabbit model of ACL reconstruction was used, and a collagen gel containing BMP-2 was injected with a syringe into the tendon–bone tunnel. It was found

Table 2 The application of hydrogel to facilitate tendon–bone healing

Intervening measure	Method of delivery	Treatment outcomes	Animal model	References
Hydrogel made with PPCs and poly ethylene glycol diacrylate tethered with BMP-2	Local injection	PPCs- BMP-2-hydrogel facilitates tendon–bone healing through fibrochondral regeneration	Rabbit rotator cuff repair model	C. H. Chen et al. [90]
Gelatin hydrogel loaded with simvastatin	Local administration	Gelatin hydrogel loaded with simvastatin can promote early tendon–bone healing	Rabbit ACL reconstruction	Oka S et al. [96]
Collagen gel loading with recombinant human BMP-2	Local injection	Collagen gel can be used as an effective carrier for BMP-2 to enter the surgical site, and can be used to enhance the healing of the tendon–bone interface	Rabbit rotator cuff repair model	Lee K W et al. [91]
FGF-2-impregnated gelatin hydrogel sheet (GHS)	Local injection	It is feasible to implant GHS impregnated with FGF-2 into rabbit bone tunnels during RC healing, and this improves both histology and biomechanics	Rabbit rotator cuff repair model	T. Tokunaga et al. [92]
Acellular lyophilized allogeneic tendon—one interfacial scaffold combined with extracellular matrix tendon hydrogel	Local administration	Acellular lyophilized allogeneic tendon–bone interfacial scaffold combined with extracellular matrix tendon hydrogel demonstrated greater repair strength and biocompatibility	Rat Achilles tendon repair model	R. McGoldrick et al. [42]
PRP combined with Gelatin Sponge (GS)	Local implanting	PRP-GS can facilitate early healing of the tendon–bone junction	Rabbit ACL reconstruction	Zhang M et al. [32]
tHG loading with ADSCs	Local injection	tHG loading with ADSCs did not significantly enhance TBI healing compared to tHG alone	Rabbit rotator cuff repair model	Y. Kaizawa et al. [93]
tHG loading with ADSCs	Local administration	tHG can induce ADSCs to locate at the site of tendon injury to enhance tendon–bone healing	Rat tendon repair model	A. Franklin et al. [89]
Chitosan/gelatin/β-glycerol phosphate(C/G/GP) hydrogel	Local administration	C/G/GP hydrogel could significantly improve tendon–bone healing in rabbit models	Rabbit ACL reconstruction	Huang Y M et al. [97]

that the fusion rate of the bone tunnel with the tissue graft was improved when collagen gel and BMP-2 mixture were combined. Besides, the application of fibroblast growth factor 2 (FGF-2) has been shown to improve the tendon–bone healing. T. Tokunaga et al. [91] investigated whether the incorporation of FGF-2 impregnated gelatin hydrogel tablets (GHT) into rabbit RC surgically repaired bone tunnels facilitated tendon–bone healing. According to the results, FGF-2 impregnation of GHT was feasible and can improve the histology and biomechanics of RC healing in rabbits. Additionally, M. Zhang et al. [32] explored the role of PRP combined with gelatin sponge (GS) in facilitating tendon–bone healing. According to the findings of this study, GS loading PRP can prolong its bioactivity time, facilitate BMSC proliferation, and facilitate osteogenic gene expression. In the rabbit model of ACL reconstruction, it also promotes the early healing process of the tendon–bone junction. The above researches demonstrate that hydrogel can be used as an effective carrier of BMP-2, FGF-2 and other cytokines entering the surgical site to facilitate the healing of the tendon–bone interface.

The researchers also found that using tHG as a stem cell carrier showed excellent repair and biocompatibility in vivo [92]. R. McGoldrick et al. [42] studied activation of acellular lyophilized allogeneic tendon–bone interface scaffolds in platelet-rich plasma, re-seeding with live ADSCs, and supplementation of extracellular matrix tendon hydrogels at implantation. The results of this study showed that the hydrogel group treated with ADSCs had the largest increase in tendon cell infiltration and fibrochondral regeneration at 8 weeks, and significantly increased type III collagen at the tendon–bone interface. These studies confirmed that tHG, as a carrier of stem cells, showed strong efficacy in facilitating tendon–bone healing. Similarly, Y. Kaizawa et al. [92] investigated whether injection of tHG loaded with ADSCs at the repair site would further promote RCT healing. However, it was found that hydrogels loaded with ADSCs did not observably improve TBI healing compared with tHG alone in a model of chronic RC injury. Based on these studies, it appears that tHG can facilitate tendon–bone healing either on its own or as a drug carrier. However, the efficacy of tHG-loaded drugs may vary due to the different operation procedures. Specific curative effects need to optimize the therapeutic strategy of the load, so as to achieve the synergistic effect of the drug and the speed of drug release, in order to achieve excellent results.

According to previous studies, simvastatin promotes osteogenesis and neovascularization [93, 94]. A study conducted by Oka et al. [95] examined the efficacy of gelatin hydrogel loaded with simvastatin in promoting angiogenesis and osteogenesis of tendon–bone healing. It has been demonstrated that low-dose simvastatin combined with gelatin hydrogel stimulates bone growth in early rabbit models by affecting angiogenesis and osteogenesis, but does not affect long-term biomechanical properties after ACL reconstruction. In addition, Y. M. Huang et al. [96] developed a chitosan/gelatin/β-glycerophosphate(C/G/GP) hydrogel, which was applied to the tendon–bone junction. Following hydrogel treatment, total bone volume and bone volume/tissue volume significantly increased compared to the control group at 8 weeks. It was also confirmed that injection of C/G/GP hydrogel could significantly improve tendon–bone healing in animal models. The above studies further confirmed that hydrogels, as excellent drug carriers, can enhance the efficacy of drugs by optimizing the release process of drugs at

the injured site. Therefore, hydrogels have great potential in the clinical application of facilitating tendon–bone healing.

Bioabsorbable interference screw

Metal interference screws can enhance early fusion of the bone tunnel and their high initial fixation strength facilitates it to withstand higher mechanical stresses [97]. However, the downside of metal screws is that they interfere with magnetic resonance imaging (MRI) and need to be removed during revision surgery [98]. Bioabsorbable screws are popular with clinicians and patients because they do not need to be removed after surgery and do not interfere with MRIs. They are non-toxic and non-tissue reactive, and degrade over time [99, 100]. Bioabsorbable interference screws are mostly composed of various biological materials. The main ones used in ACL reconstructive surgery are poly-levo/β-tricalcium phosphate biocomposite interference screw, β-tricalcium phosphate/poly-levo/tricalcium phosphate biocomposite interference screw, polyether-ether-ketone related biocomposite interference screw, polyether-ether-ketone related biocomposite interference screw and biodegradable high-purity magnesium screw [101–106] (Fig. 3). Biodegradable screws have been widely used by researchers in tendon fixation during ACL reconstruction. A great many preclinical and clinical studies have confirmed their efficacy in facilitating tendon–bone healing (Table 3), indicating that the application of absorbable biological screws has certain clinical application potential in ACL reconstruction.

To assess the side effects of the biocompound interference screw, the researchers monitored its degradation in vivo through clinical studies. F. A. Barber et al. [101] evaluated the long-term degradation of biocomplex interference screws synthesized with poly (96%)/dextran (4%)-lactic acid/tricalcium β-phosphate (PL/D-LA/β-TCP). In this study, eight patients underwent ACL reconstruction using PL/D-LA/β-TCP biocomposite interference screws and biological monitoring in vivo. In this study, it was found that the screw was replaced 4 years after reconstructing the ACL by calcified non-trabecular material. Bone conductivity was demonstrated at 71% of screw sites, and 33% of screw

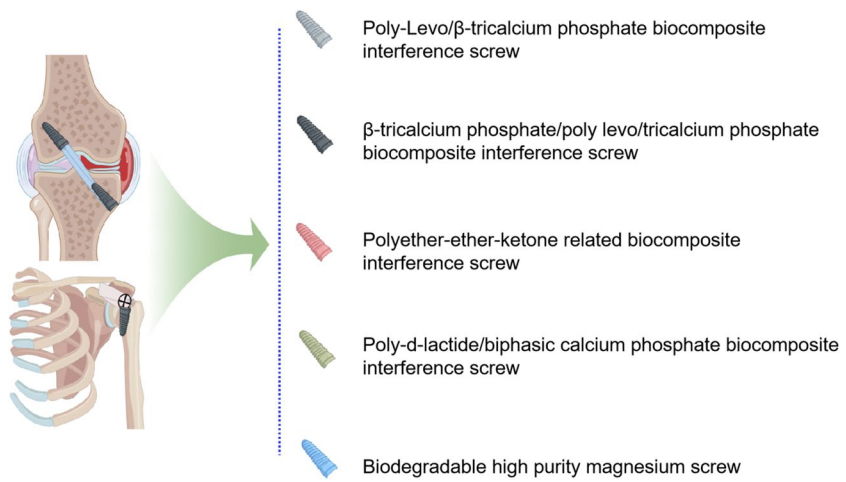

Fig. 3 This figure shows the type of bioabsorbable interference screw used for tendon fixation during ACL reconstruction. This figure was created by Figdraw

Table 3 The application of bioabsorbable interference screw to facilitate tendon–bone healing

Intervening measure	Method of delivery	Treatment outcomes	Animal model	References
Interference screw made with poly-levo /dextro-lactide/β-tricalcium phosphate	Local implanting	The interference screw was replaced with calcified non-trabecular material and osteoconductive 4 years after ACL reconstruction	Patient ACL reconstruction	F. A. Barber et al. [102]
Biodegradable HP Mg screw	Local implanting	HP Mg screw improved biomechanical properties of grafts in the early stage of tendon healing	Rabbit ACL reconstruction	Cheng P et al. [107]
Biodegradable HP Mg screw	Local implanting	HP Mg screw has the potential to promote the regeneration of fibrocartilage implants in ACL reconstruction	Rabbit ACL reconstruction	Cheng P et al. [62]
Mg-based interference screw	Local implanting	The optimization of the structure and function of the tendon–bone interface may be due to the enhancement of cell migration and adhesion strength under the stimulation of Mg ions degraded by Mg screws implanted	Rabbit ACL reconstruction	J. Wang et al. [114]
Biodegradable Magnesium Screws	Local implanting	In addition to being corrosion-resistant, magnesium screws can promote tendon and bone healing	Rabbit ACL reconstruction	Wang J et al. [115]
MILAGRO bioabsorbable interference screws	Local implanting	Application of MILAGRO bioabsorbable interference screws do not lead to tunnel widening after ACL reconstruction	Patient ACL reconstruction	K. Shiwaku et al. [104]
Biocomposite interference screw	Local implanting	The screws were replaced by calcified bone trabeculae an average of 42 months after implantation	Patient ACL reconstruction	F. A. Barber et al. [103]
Bioabsorbable interference screw	Local implanting	The rate of bone resorption and bone replacement was high 2–5 years after the application of this biological screw, and the tunnel size did not increase	Patient ACL reconstruction	B. Scrivens et al. [105]

Table 3 (continued)

Intervening measure	Method of delivery	Treatment outcomes	Animal model	References
Bioabsorbable screw	Local implanting	95.0% of the patients had better knee joint condition than before operation, and 95.0% of the patients were satisfied with the operation results	Patient ACL reconstruction	I. Khan et al. [106]

sites were almost completely filled with bone. The study also confirmed that PL/D-LA/β-TCP biocomposite interference screw has bone conduction properties. Similarly, F. A. Barber et al. [102] evaluated the long-term degradation of micro β-tricalcium phosphate polylevo-dextral (96%)/dextral (4%) lactate-tricalcium phosphate biocomposite interference screws in vivo. Twenty patients underwent ACL reconstruction, fixation of the femur and tibia with these biocomposite screws, and were followed for at least 36 months. The results confirmed that micro β-tricalcium phosphate poly-L-(96%)/right-handed (4%) lactide-tricalcium phosphate interference screws were replaced by calcified non-trabecular materials in the ACL reconstruction model at an average of 42 months after implantation. Bone conductivity was also demonstrated in this study. These studies suggest that the use of biocomposite screws in ACL reconstruction can indeed be absorbed and replaced by calcified bone tissue over a certain period of time.

In addition, K. Shiwaku et al. [103] studied the effect of bioabsorbable interference screws on tunnel enlargement after ACL reconstruction. Femoral fixation with rectangular tunnel ACL reconstruction was performed using MILAGRO Bioabsorbable interference screw. Forty-six patients were enrolled in this prospective study and underwent CT scans at 2 weeks and 1 year after surgery. The results of this study found that no tunnel widening was observed by computed tomography analysis at 2 weeks and 1 year after the ACL reconstruction with a bioabsorbable interference screw for femur fixation. Similarly, B. Scrivens et al. [104] evaluated the widening and absorption of femoral and tibial tunnels with screws composed of 30% biphasic calcium phosphate and 70% poly-d-lactide (BCP/PLDLA) 2 to 5 years after ACL reconstruction. The study included 20 patients with ACL reconstruction and was reevaluated using computed tomography 2 to 5 years after surgery. This study found that BCP/PLDLA interfering screws for ACL reconstruction had a high rate of bone resorption and bone replacement 2 to 5 years after surgery, and no increase in tunnel size. These studies suggest that bioabsorbable interference screws facilitate tendon–bone healing without increasing the expansion of bone tunnels. In addition, some investigators have attempted to use internal fixation screws to support the graft in the femur and bioabsorbable interference screws in the tibia during ACL reconstruction [105]. In the end, 95.0% of the patients' knee joint condition was better than that before surgery, and 95.0% of the patients were satisfied with the results of surgery. This study suggests that a personalized tendon–bone fixation for different individuals can also lead to better patient satisfaction.

Over the past few decades, the application of biodegradable magnesium (Mg) in the field of orthopedics has attracted considerable interest from materials engineers and

clinicians [107–111], thus raising hopes for successful solutions to current commercial interference screw defects. Magnesium and its alloys have good biocompatibility and stiffness, indicating that they are suitable as promising orthopedic implants [112]. In recent years, a number of studies have reported the beneficial effects of magnesium implants on fracture healing, suggesting the potential application of magnesium implants in promoting the integration of tendon grafts. Cheng P et al. [106] studied bone graft degradation and screw corrosion using biodegradable high-purity magnesium (HP Mg) screws in rabbit ACL reconstruction model. The biomechanical properties of tendon grafts fixed with HP Mg screws were significantly better than those of Ti screws in this study. When the grafts were severely degraded by histological analysis at 3 weeks, tendon grafts in the HP Mg screws group showed significantly better biomechanical properties than those in the titanium nail group, and the relative area of collagen fibers at the tendon–bone interface was larger. This study demonstrated that Mg screws inhibited graft degradation and improved biomechanical properties of grafts during early tendon healing, highlighting their potential in ACL reconstruction. Later, Cheng P et al. [62] confirmed that biodegradable HP Mg had good cytocompatibility and promoted tendon–bone healing by promoting the expression of BMP-2 and VEGF in a rabbit ACL reconstruction model. Similarly, J. Wang et al. [113] developed a magnesium-based interference screw for tendon graft fixation of ACL reconstruction and investigated its biological role in promoting graft healing in bone tunnel. It has been demonstrated that magnesium-based interference screws promote BMSC chemotactic migration into bone tunnels, potentially due to the upregulation of local TGF-β1 and PDGF. Furthermore, higher Mg ion concentration has been shown to improve BMSC adhesion and osteogenic differentiation in vitro. Therefore, the application of magnesium-based interference screws facilitates the enhancement of cell migration, cell adhesion and osteogenic differentiation of BMSCs, thereby improving the healing of the tendon–bone interface. J. Wang et al. [114] also compared the effects of Mg screws and Ti screws on the healing of tendon grafts in rabbits with ACL reconstruction. It was found that the Mg screw significantly improved the healing quality of the transplanted tendon by encouraging the mineralization of the tendon graft end. In addition, magnesium screw showed good corrosion resistance, and the degradation of magnesium screw did not cause the enlargement of bone tunnel. The above studies suggest that Mg screws can facilitate tendon–bone healing after ACL reconstruction, suggesting a potential substitute for titanium screws in clinical applications.

Future perspectives

In summary, the success of tendon/ligament reconstruction surgery hinges on the graft's fusion with the bone tunnel. Various biological strategies, including growth factors [22], PRP [23], cells from different sources [24, 25], and biomaterials [27, 28], have shown potential in preclinical studies. However, their individual efficacy is limited. Combining biomaterials with other strategies has yielded promising results [39–43].

Looking ahead, several emerging directions warrant further exploration to advance tendon–bone healing research. First, the development of smart biomaterials with stimuli-responsive properties (e.g., pH-, temperature-, or mechano-sensitive hydrogels) could enable dynamic modulation of the healing microenvironment[115]. For instance,

4D-printed scaffolds that adapt to mechanical loading or biochemical cues post-implantation may better mimic the natural tendon–bone interface's gradient structure [116]. Second, personalized bioengineering strategies leveraging patient-specific cells (e.g., induced pluripotent stem cells) or gene-editing technologies (e.g., CRISPR–Cas9) could address individual variability in healing capacity [117, 118]. Recent studies highlight the potential of exosome-loaded scaffolds to deliver targeted miRNAs or growth factors, enhancing angiogenesis and osteogenesis without exogenous cell transplantation [119, 120].

Integrating advanced manufacturing techniques like electrospinning with multi-omics profiling (e.g., transcriptomics, proteomics) could optimize scaffold design by identifying critical molecular pathways driving fibrocartilage formation [121]. Additionally, the application of artificial intelligence (AI) in predicting optimal cytokine release kinetics or scaffold degradation rates may accelerate the translation of combinatorial therapies [122]. Furthermore, addressing the long-term biocompatibility and immunogenicity of degradable materials, such as magnesium alloys or polymer composites, remains crucial. While Mg screws demonstrate osteoconductive properties [62, 110], their rapid degradation in vivo necessitates surface modification or alloy development to balance corrosion resistance and bioactivity [123].

However, current research in this field also has some limitations. For example, the complex biological environment in vivo may affect the performance of bioengineered materials, and the long-term effects of these materials on tendon–bone healing need further investigation [33]. Additionally, the manufacturing process of some advanced biomaterials is still challenging, and the cost and accessibility of these technologies need to be considered for clinical translation [70]. Finally, the ethical and regulatory issues associated with the use of gene-editing technologies and patient-specific cells require careful evaluation [117].

Finally, bridging the gap between preclinical models and clinical trials requires standardized outcome metrics and larger cohort studies. For example, longitudinal imaging technologies (e.g., micro-CT coupled with AI-based analysis) could non-invasively monitor scaffold integration and fibrocartilage maturation in humans [124]. Collaborative efforts among material scientists, clinicians, and bioengineers will be pivotal in overcoming current limitations and achieving functional restoration of the tendon–bone interface.

Conclusions

In summary, biomaterials play a crucial role in tendon–bone healing after RC and ACL injuries. Current strategies, including tissue engineering scaffolds and hydrogels, show promise in enhancing healing. Future research should focus on developing smart biomaterials, personalized approaches, and advanced manufacturing techniques to improve clinical outcomes.

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