Biomaterials Translational

Biological approaches to the repair and regeneration of the rotator cuff tendon-bone enthesis: a literature review

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Key Words:
enthesis; rotator cuff; stem cells; tissue engineering; tendon-bone enthesis

From the Contents

ABSTRACT

Entheses are highly specialised organs connecting ligaments and tendons to bones, facilitating force transmission, and providing mechanical strengths to absorb forces encountered. Two types of entheses, fibrocartilaginous and fibrous, exist in interfaces. The gradual fibrocartilaginous type is in rotator cuff tendons and is more frequently injured due to the poor healing capacity that leads to loss of the original structural and biomechanical properties and is attributed to the high prevalence of retears. Fluctuating methodologies and outcomes of biological approaches are challenges to overcome for them to be routinely used in clinics. Therefore, stratifying the existing literature according to different categories (chronicity, extent of tear, and studied population) would effectively guide repair approaches. This literature review supports tissue engineering approaches to promote rotator cuff enthesis healing employing cells, growth factors, and scaffolds period. Outcomes suggest its promising role in animal studies as well as some clinical trials and that combination therapies are more beneficial than individualized ones. It then highlights the importance of tailoring interventions according to the tear extent, chronicity, and the population being treated. Contributing factors such as loading, deficiencies, and lifestyle habits should also be taken into consideration. Optimum results can be achieved if biological, mechanical, and environmental factors are approached. It is challenging to determine whether variations are due to the interventions themselves, the animal models, loading regimen, materials, or tear mechanisms. Future research should focus on tailoring interventions for different categories to formulate protocols, which would best guide regenerative medicine decision making.

http://doi.org/10.12336/biomatertransl.2023.02.004

How to cite this article:
Abdalla, A.; Pendegrass, C. Biological approaches to the repair and regeneration of the rotator cuff tendon-bone enthesis: a literature review. *Biomater Transl.* **2023**, *4*(2), 85-103.

Introduction

Entheses are highly specialised interfaces between fibrous isotropic tendons and ligaments (elastic modulus = 450 MPa axially) that provide tensile strength, and rigid inelastic isotropic bones (elastic modulus = 20 GPa) that optimise compressive loads, facilitating joint motion.[1] Entheses evolved highly specialised structures that effectively dampen the forces encountered in the region of peak strain, to facilitate seamless stress transfer and prevent tendon avulsion; whilst maintaining effective communication between tendons and bones to preserve homeostasis.[2-4] This heterogenous interface is unique and owing to its complexity and propensity to heal with biomechanically inferior scar tissue, presents significant challenges to repair and regeneration.

Rotator cuff (RC) tears are common with an increasing prevalence of partial and full thickness tears after the age of 50, and a 90% surgical repair failure.[5-7] The capacity to repair the damaged enthesis is insufficient, because of the tissue's lack of regeneration, leading to scar formation with inferior mechanical properties at the repair site.[8] Trials to enhance the healing progress of the RC enthesis have been directed towards

regenerative methods.[7] To date, there are no records of a single successful clinical biological approach achieving an enhanced healing of the injured enthesis. This review investigates the potential use of tailored biological therapies in different RC tear mechanisms, chronicity, and populations treated.

Entheses types

Histologically, there are two types of entheses classified according to the presence or absence of fibrocartilage, Fibrocartilaginous and Fibrous. Fibrous entheses insert via collagen fibres at the metaphysis or diaphysis to dissipate load over a large area, such as the deltoid and the medial collateral ligament, while fibrocartilaginous are at the epiphyses of long bones, such as the RC and Achilles tendons.[9, 10] The fibrocartilage of fibrocartilaginous entheses is not distributed evenly throughout the interface; appearing thickest in the deepest layers and absent superficially, consistent with the highest stress distribution.[11, 12] Fibrocartilaginous entheses, such as the RC, are more commonly injured and will therefore be the focus of this review.[13]

Entheses microstructure

Fibrocartilaginous entheses comprise four layers: dense fibrous tendon, fibrocartilage, mineralised fibrocartilage, and bone. The layers gradually increase in stiffness from tendon to bone to distribute forces over wider surface areas. The first level is composed of organised parallel appearance of collagen I and low levels of Proteoglycans within interspaced elongated tendon fibroblasts. The non-mineralised layer is populated with rows of round fibrochondrocytes embedded in a collagen II- and III-rich extracellular matrix (ECM), and low levels of collagen X, proteoglycans, and glycosaminoglycans. The fibrocartilage and mineralised fibrocartilage regions are separated by a tide mark. The mineralised fibrocartilage merges into bone, which consists of osteoblasts, osteocytes, and osteoclasts, alongside collagen I and a 69% elevated mineral content of which 99% is hydroxyapatite.[14]

The progressive structure and composition of entheses allow minimisation of the mechanical vulnerability that would arise due to the large elastic modulus mismatch. The structural and mechanical properties of entheses are a result of mechanical loading that have an essential role in enthesis maturation, allowing load transmission and stress reduction.[14] This highlights the importance of developing repair solutions that mimic the native biological and mechanical integration of entheses.

Entheses mechanical properties

Force transmission via the enthesis dynamically involves fibre realignment, crimp deformation, and sliding, which are essential for remodelling and turnover. Fibrocartilage enthesis acts like a stretch break that limits tendon narrowing at the insertion, which is a region of stress concentration, hence tendons cross-sectional area increases as they insert into the bone.[15, 16] The unmineralised region resists compression, while the mineralised resists shearing, creating a two-layered protective component.[17] Levels of unmineralised fibrocartilage are higher at entheses with more varied ranges of insertion angles, highlighting its functional role. The mineralised fibrocartilage attachment into bone is rather atypical, providing entheses with varied mechanical integrity.[14] Owing to the complex structure of the enthesis; when damaged, it is extremely challenging to repair surgically. The functionally gradual layers are not restored after repairs and the subsequent healing process.[2, 18, 19]

Entheses embryological development

Embryologically, it has been hypothesised that initially hyaline cartilage at the enthesis exists alone, and tendons attach to it. The cartilage erodes from the bone and is replaced by the fibrocartilaginous enthesis akin to a growth plate. This emphasises the fibrocartilaginous enthesis development within the tendon.[20,21] *In utero*, the enthesis is originally organised as an unmineralised cartilaginous unit that is mineralised postnatally by endochondral ossification.[22-24] Transcription factors, such as SRY-box 9, have been found essential for chondrogenesis, and others for tenogenesis such as mohawk and scleraxis.[25-27] Scleraxis knockout mice demonstrated a lower bone mineral density, decreased attachment strength, and disorganised collagen fibres.[23,28] Growth factors (GFs), such as transforming growth factor-beta (TGF-β) and bone morphogenetic protein (BMP) are regulators in early enthesis formation, and molecules such as Indian hedgehog (Ihh) and parathyroid hormone-related protein regulate late mineralisation.[22, 23, 29-31] During early development, enthesis progenitor cells proliferate and lengthen it, and express collagen I. Stimulated by BMP-4 and Ihh, at the base of the developing enthesis, the cells differentiate into unmineralised fibrochondrocytes, and express collagen I and II. By stimulation of Ihh at the postnatal stage, fibrochondrocytes undergo hypertrophic differentiation at the base of the enthesis. As the mineralised fibrochondrocytes form, collagen X and alkaline phosphate are expressed.[32]

Since tissue distortion and decreased mineralisation are seen in paralysed mice models, muscle loading is essential for the developing enthesis maturation alongside molecular components.[33-35] Disordered cell patterns and lack of enthesis regional transition are effects of reduced muscular stress during development.[36, 37] A balance between GFs and mechanical stimulation gives rise to the mature complex enthesis structure and composition.

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Rotator cuff enthesis and scar tissue

High rates of RC retears are well documented, where various improved suture techniques have been ineffective in reducing them.[38] Surgical repairs for RC tears are often performed via a single or double row suture technique with the aim of approximating the ruptured soft tissue segment from bone. However, due to factors such as age, tear chronicity, and poor vascularity, high retear rates persist with scar-mediated tissue of disorganised matrix and inferior mechanical properties forms.[7, 19, 39-42] Scar formation is thought to be a result of TGF-β1 production by macrophages during the inflammatory phase, leading to fibroblast recruitment.[43] Since expression of TGF-β is elevated at injured entheses, it increases collagen I and III deposition and inhibits chondrogenic differentiation.[19]

Factors influencing healing

Despite better outcomes being linked to intact repairs, it does not guarantee patient satisfaction with functional outcomes.[44,45] Variables affecting outcomes of RC repairs include (I) Age: decrease in turnover, fatty infiltration and tear retraction are thought to be the cause for altering the enthesis healing in older populations regardless of the surgical procedure used.[46-51] (II) Muscle atrophy: severe pre-operative atrophy and fatty infiltration were linked to lower post-operative repair integrity.[45, 52, 53] (III) Smoking: nicotine has been linked to impairments in biomechanical properties and delayed healing.[54] (IV) Diabetes and hypercholesterolemia: they have shown to reduce RC enthesis mechanical properties.[55] Additionally, diabetes increased post-operative complications, such as infections and failures after RC repairs, while hypercholesterolemia increased tendon-related pathologies.[56,57] (V) Obesity demonstrated inferior mechanical properties and poorer histological outcomes with high fat diet.[58] This suggests that long-term maintenance of dietary intake to manage lipid levels and blood glucose prior to injury might have a positive influence on the healing process. (VI) Contrasting evidence exists regarding the effect of vitamin D levels on RC enthesis healing. Animal studies suggest a negative influence of low vitamin D on RC repair, while clinical trials found no correlation between vitamin D levels and retear rates.[59, 60] However, a large clinical study of arthroscopic RC repair found bone mineral density to be a reliable indicator of RC recovery.[61] (VII) Non-steroidal anti-inflammatory drugs: they negatively affect healing in the acute post-operative stage for up to 6 weeks, while positively on remodelling of collagen matrix in chronic stages.[62, 63]

Methodology

An electronic database search was performed using UCL's Online Library Service and PubMed. Keywords used were "enthesis AND rotator cuff", "rotator cuff AND tear", "rotator cuff OR enthesis", "tissue engineering AND rotator cuff", "stem cells AND rotator cuff enthesis", and "growth factors AND rotator cuff enthesis". Outcomes of *in-vivo*, *in-vitro*, and clinical studies on RC enthesis repair involving various tear extent, mechanism, chronicity, and population studies were also included. Exclusion criteria included other types of entheses, and surgical and rehabilitative interventions.

A total of 59 relevant studies were found after exclusion criteria were applied. Of these, 45 presented positive, 10 negative, and 4 mixed findings.

Literature was then summarised based on three main interventions: stem cells, GFs, and scaffolds. Findings were then categorised into groups according to their findings and methodologies (acute-full, chronic-full, acute-partial, chronic-partial, in aging and younger populations, and *in-vitro* studies). **Figure 1** summarises the methodology process.

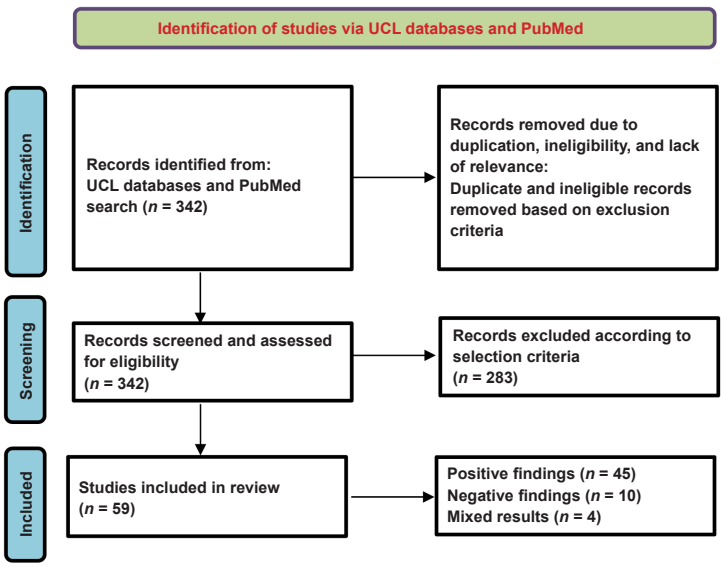

Figure 1. A flowchart representing selection stages of the studies for their inclusion in the literature review.

Literature Review Findings

Cells and rotator cuff enthesis healing

Various stem cells such as mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs), and bone marrow MSCs (BMSCs) are under investigation for potential use in enthesis regeneration.[64]

Mesenchymal stem cells

RC enthesis repairs could benefit from MSCs' capacity for self-renewal and multipotency, their availability, accessibility, and low immunogenicity.[65] Moreover, MSCs' local synthesis of GFs may improve the environment for healing.[66] Animal model studies have proven MSCs' potential for increasing ultimate load failure and resistance to mechanical deformation, enhancing bone quality, and attracting new fibrocartilage formation at the repaired site.[67] Additionally, exogenous hyaluronic acid and MSCs have been showing promising potential to reduce retears.[68]

Bone marrow mesenchymal stem cells

BMSCs enhanced structural integrity of the repair and decreased the risk of retears in a chronic full tear cohort that underwent arthroscopic RC surgery with repeated channelling.[69] Moreover, partial tear BMSC-enhanced repairs and prevented retears in 10-year follow-ups.[70] Additionally, arthroscopy surface holding with BMSC stimulation increased RC repair integrity in large chronic tears.[71] BMSCs stimulated by bioactive factors were more effective in promoting tissue regeneration. Platelet-rich plasma (PRP)-infused BMSCs improved GF production, osteogenic differentiation capacity, cell death resistance *in-vitro*, and biomechanical properties of newly formed bone *in-vivo*.[72] Conversely, structure, composition, and strength of the repaired enthesis remained unchanged, despite BMSCs being present and active metabolically.[73] However, this may be due to the short time taken to conduct the study, since stem cells require a longer time to be effective.[74] Moreover, adenoviral MT1-matrix metalloproteinase (MMP)-augmented MSCs resulted in better fibrocartilage formation, and higher ultimate load and stress to failure after 4-week repair of acute full tears, while long-term effects require further research.[75]

Adipose-derived stem cells

ADSCs have a comparable shape and expression of the cluster differentiation surface marker protein to BMSCs with greater colony-forming and adipogenic capacity. They demonstrated multipotency *in-vitro*; developing into adipose, osteogenic, chondrogenic, and myogenic cells.[76] Four groups were compared in a chronic full rabbit repair model: saline + suture, suture + ADSCs, saline, and ADSCs. ADSC and saline groups failed to heal, while suture + ADSCs group had a larger load to failure and less fatty infiltration than saline + suture group.[77] Moreover, ADSCs imbedded in a fibrin sealant resulted in superior histological and biomechanical outcomes, in acute full murine RC repairs.[78] As for the ideal location to deliver cells, regeneration was found most effective when stem cell sheets were interposed at the enthesis, in chronic full tears.[79]

In contrast, ADSCs in acute and chronic rat RC reconstruction models did not enhance biomechanical characteristics. However, inflammation was reduced, which could potentially lead to a more elastic repair and less scar formation after the healing process.[80] Furthermore, TGF-β3 supplementation did not enhance ADSCs' effect on healing, despite its known role in the development of the enthesis.[81] The absence of other mediators that are present during development and the presence of inflammatory mediators may have affected the bioactivity of TGF-β3 at the repair time. However, this study did not measure healing at different time points and ADSCs were not labeled to permit analysis of cell retention.

Due to contradictory evidence, it is unclear whether ADSCs constitute a good option to speed RC tendon-bone healing. To demonstrate its value in RC healing, more animal and clinical research is required. Additionally, challenges of availability, seeding, survival, and specificity of such therapies and the ethical regulatory barriers are yet to be overcome for this to reach a clinical trial. **Table 1** summarises the findings.

Cell pathways and rotator cuff enthesis healing

Ihh signaling molecule

Ihh signaling is active during the initial phases of RC enthesis healing.[29, 82, 83] Fibrocartilage production in an acute full rat RC repair model had higher numbers of Ihh chondrocyte-like cells with MSC augmentation. Increased GLI family zinc finger 1 (Gli1) and Patched1 expression suggests that Ihh signaling pathway controls fibrocartilage production process brought on by stem cells. While both are expressed in fibroblasts of the tendon mid-substance, Ihh is primarily expressed in chondrocytes of the fibrocartilage region, which may indicate a coordinated interaction between chondrocytes and fibroblasts during healing.[82] Additionally, immature mice with acute partial tears had a better recovery than adult mice due to the increased density of $Gli1^+$ cells near the injured enthesis, mimicking its natural developmental process.[83]

Parathyroid hormone related protein

Parathyroid hormone (PTH) has been demonstrated to enhance tissue repair via a chondrogenic pathway.[84, 85] Osteoblasts speed up tendon-bone healing when PTH binds to its receptor in BMSCs during the tendon-bone healing process. Chen et al.[86] showed that PTH may influence the tendon-bone healing process by maintaining the proliferation of BMSCs.

Daily systemic PTH injections boosted fibrocartilage development, type-I procollagen-producing cells, and vascularity, which improved collagen fibre structure and mineralised fibrocartilage production in acute full RC tears.[87] Biomechanically, Duchman et al reported higher load to failure in recombinant human PTH-treated acute full RC tear rat model, and expression of intracellular and extracellular vascular endothelial growth factor (VEGF) with controlled recombinant human PTH systemic injections.[88] Clinical investigations of advanced cases with chronic large tears achieved similar outcomes, and reduced retear rates.[89] **Table 2** summarises the findings.

Table 1. Summary of cell-based therapies literature findings

Author	Study	Model	Tear	Intervention	Outcome measure	Results
Honda et al.[68]	*In-vivo*	Rabbit	Chronic full	MSC + HA	Biomechanical, histological, and immunohistochemical analyses	Positive: Improved ultimate load and faster healing
Jo et al.[69]	Clinical	Human	Chronic full	BMSC + arthroscopic repeated channeling	Pain scale, ROM, muscle strength, patient satisfaction questionnaire, and functional scores. Structural integrity by MRI and CT	Positive: Enhanced structural integrity of the repair and decreased retears
Hernigou et al.[70]	Clinical	Human	Chronic partial	BMSC + arthroscopy	MRI	Positive: Faster complete healing/retear prevention
Taniguchi et al.[71]	Clinical	Human	Chronic partial	ASH + BMSC	MRI	Positive: Reduced retear rates/better integrity
Han et al.[72]	*In-vitro*, *in-vivo*	Rat	Acute full	PRP-infused BMSC	Expression of genes that related to tissue repair, bone formation, and tendon regeneration;	Positive: Stronger signals to angiogenesis, bone formation, and tendon generation *in-situ*
					Biomechanical assessment	Promoted healing *in-vivo*
Gulotta et al.[73]	*In-vivo*	Rat	Acute full	BMSC	Biomechanical & histological analyses	Negative: No change in structure, composition, or strength
Gulotta et al.[75]	*In-vivo*	Rat	Acute full	MT1-MMP-transduced MSCs	Biomechanical & histological analyses	Positive: Better fibrocartilage formation, higher ultimate load and stress to failure, and higher stiffness
Oh et al.[77]	*In-vivo*	Rabbit	Chronic full	ADSC + suture	Electromyographic, biomechanical & histological analyses	Positive: Larger load to failure and less fat infiltration
Chen et al.[78]	*In-vivo*	Murine	Acute full	ADSC imbedded in fibrin sealant scaffold	Biomechanical & histological analyses	Positive: Better biomechanical strength and histological score
Choi et al.[79]	*In-vivo*	Rat	Chronic full	ADSC sheets interposed at the enthesis	Biomechanical & histological analyses	Positive: Successful complete regeneration and biomechanical strength
Valencia Mora et al.[80]	*In-vivo*	Rat	Chronic full	ADSC, ADSC + TGF-β3	Biomechanical & histological analyses	Positive: Reduced inflammation
						Negative: Unchanged maximum load, elastic energy, mechanical deformation, and stiffness

Note: ADSC: adipose-derived stem cell; ASH: arthroscopy surface holding; BMSC: bone marrow mesenchymal stem cell; CT: computed tomography; HA: hyaluronic acid; MMP: matrix metalloproteinase; MRI: magnetic resonance imaging; MSC: mesenchymal stem cell; PRP: platelet-rich plasma; ROM: range of motion; TGF: transforming growth factor.

Growth factors

GFs have been investigated to modulate stem cells in RC enthesis of small and large animal models.[90-96] Fibroblast growth factor 2 (FGF-2), growth differentiation factor, TGF-β3, and platelet-derived growth factor are commonly used examples.[97-104] GFs such as BMP-12, -13, -14, basic fibroblast growth factor, cartilage oligomeric matrix protein, connective tissue growth factor, platelet-derived growth factor-B, and TGF-β1 have been found to be involved in enthesis healing process, one week after acute full rat supraspinatus repair. By 16 weeks, GF upregulation was back to pre-injury levels, indicating exogenous supplementation of these substances may encourage successful healing in acute stages.[105] Angiogenesis and fibroblast proliferation are both powerfully stimulated by basic fibroblast growth factor. It continues to be strongly exhibited throughout the healing process, peaking at 7 and 9 days.[106] Similar outcomes were attained in acute full sheep model RC tear, where BMP and VEGF induced angiogenesis and vasculogenesis, causing faster and better recovery.[43, 107]

Studies investigated TGF-β3's potential to push scar-mediated healing to a regenerative one.[108-111] Sustained delivery of TGF-β3 via a heparin/fibrin-based system in a rat model improved RC enthesis healing, while still inferior to an uninjured enthesis and disorganised scarring.[110] Conversely, studies reported no improvement in biomechanical properties

Table 2. Summary of signaling molecules therapies literature findings

Author	Study	Model	Tear	Intervention	Outcome measure	Study results
Zong et al.[82]	*In-vivo*	Rat	Acute full	Ihh + MSC	Immunohistochemical staining and proliferating cell nuclear antigen staining	Positive: Increased Gli1 and Patched1 expression. More organised and stronger staining for collagen II
Schwartz et al.[29]	*In-vivo*	Murine	Acute partial	Ihh	Lineage tracing	Positive: Gli1 lineage cells that originate in utero eventually populate the entire mature enthesis. Ablation of the Hh-responsive cells during the first week of postnatal development resulted in a loss of mineralised fibrocartilage
Schwartz et al.[83]	*In-vivo*	Mouse	Acute partial	Ihh	Lineage tracing	Positive: High levels of Gli1 expression in immature mice and mature entheses had fewer $Gli1^{+}$ cells
Hettrich et al.[87]	*In-vivo*	Rat	Acute full	Systemic PTH	Histologic, immunohistochemical, biomechanical analyses	Positive: Higher stiffness, bone volume and mineral content; More fibrocartilage, osteoblasts, and blood vessels formation; Better collagen orientation
Duchman et al.[88]	*In-vivo*	Rat	Acute full	Systemic rhPTH	Biomechanical and histologic analysis	Positive: Higher load to failure. Expression of intracellular and extracellular VEGF
Oh et al.[89]	Clinical	Human	Chronic full	Systemic rhPTH	MRI, ROM, American Shoulder and Elbow Surgeons and Constant scores, and simple shoulder test	Positive: Lower retear rate

Note: Gli1: GLI family zinc finger 1; Hh: hedgehog; Ihh: Indian hedgehog; MRI: magnetic resonance imaging; MSC: mesenchymal stem cell; PTH: parathyroid hormone; rhPTH: recombinant human parathyroid hormone; ROM: range of motion; VEGF: vascular endothelial growth factor.

or scar reduction, with TGF-β3 and neutralising bodies for TGF-β1 and -β2 delivered via osmotic pumps, while inhibiting TGF-β1 improved RC enthesis quality by reducing fibrosis, fatty infiltration, and muscle atrophy.[108, 112] This however may be due to the delivery method used in the study, as antibodies were not delivered directly to the interface, rather to the bursal surface. Additionally, TGF-β1 release could compete for receptors with TGF-β3, which leads to reduced effectiveness of TGF-β3 treatment. A suggested solution is to combine TGF-β3 with a cytokine antagonist and TGF-β-neutralising antibodies or MMP inhibitors for acute full tears.[32]

Recombinant human FGF-18 was investigated for chondrogenic differentiation of BMSCs in a rat acute full tear model and enhanced regeneration in acute full RC tears.[113] Furthermore, tumour necrosis factor (TNF) cytokine has been found to suppress chondrogenic stimulation via nuclear factor-kappa B by downregulating SRY-box 9 expression, whilst TGF-β3 solely was not ideal.[114] While TNF inhibitor pegylated soluble TNF-R1 increased fibrocartilage and enhanced load to failure and stiffness, no improvement was seen past 8 weeks.[115]

Since loading after RC repairs is essential to prevent bone loss at the enthesis attachment, to achieve a mechanically resilient enthesis, collagen fibres within the tendon must attach to bone via mineralised fibrocartilage and remodel the underlying bone.[30, 116] Hence, osteoinductive factors (BMP-2–7) are used to induce chondrogenic differentiation and stimulate ECM component synthesis such as proteoglycans and collagen-II. Additionally, BMP-7 improved enthesis matrix maturation in gelatin hydrogel sheets of acute full RC tears.[117, 118] Conversely, Rodeo et al.[107] implanted TGF-β1–3, BMP-2–7, and FGF in a collagen I matrix sponge and compared it to collagen sponge alone, in a sheep acute RC repair. While the study reported greater bone, fibrocartilage, and soft tissue formation, stiffness was less than collagen sponge only group.[107] Although frequently having superior mechanical properties compared to controls, GF-enhanced repairs lack identical biomechanical qualities as native entheses.

GF temporal expression

Despite being present in all stages of healing, GF signal different pathways with different cell types during each stage. BMP-12, -13, -14, bFGF, connective tissue growth factor, platelet-derived growth factor, TGF-β1, and cartilage oligomeric matrix protein-1 are upregulated at the initial inflammatory stage, and subside by 16 weeks.[105] The delay of TGF-β1 upregulation at 8 weeks is correlated with scar formation process.[119] However, BMP-12 is expressed during all three phases, with a marked increase at eight weeks of remodelling stage. This highlights

GF temporal expression involved in various stages of healing, which is essential in developing GFs delivery devices that can be introduced to spatiotemporally target RC repairs. Since healing process is regulated by multiple GFs, targeting one is not ideal functionally or mechanically.[105] **Table 3** summarises the findings.

Table 3. Summary of growth factor-based therapies literature findings

Author	Study	Model	Tear	Intervention	Outcome measure	Study results
Würgler-Hauri et al.[105]	*In-vivo*	Rat	Acute full	BMP-12–14, bFGF, COMP, CTGF, PDGFB, TGF-β1	Immunohistochemical staining	Positive: Increase in the expression of all GFs at 1 week, and followed by a return to control or undetectable levels by 16 weeks
Kobayashi et al.[106]	*In-vivo*	Rabbit	Acute full	BMP-12–14, bFGF, COMP, CTGF, PDGFB, TGF-β1	Light microscopy after staining with hematoxylin-eosin and Elastica-Masson; Immunohistochemical staining	Positive: GFs are involved in early phases of healing promotion
Rodeo et al.[107]	*In-vivo*	Sheep	Acute full	BMP and VEGF	MRI, plain radiographs, histologic analysis, and biomechanical testing	Positive: Greater formation of new bone, fibrocartilage, and soft tissue, with an increase in tendon attachment strength
Angeline and Rodeo[43]	*In-vivo*	Sheep	Acute full	BMP and VEGF	Histologic analysis	Positive: Induced angiogenesis and vasculogenesis. Faster and better recovery
Manning et al.[110]	*In-vivo*	Rat	Acute full	TGF-β3	Histologic and biomechanical analyses	Negative: Disorganised scar and inferior mechanical properties
Kim et al.[108]	*In-vivo*	Rat	Acute full	TGF-β3	Histologic and biomechanical analyses	Negative: Disorganised scar and inferior mechanical properties
Davies et al.[112]	*In-vivo*	Mouse	Acute full	Inhibiting TGF-β1	Histologic analysis	Positive: Reduced fibrosis, fatty infiltration, and muscle atrophy
Jensen et al.[32]	*In-vivo*	Mouse	Acute full and partial	TGF-β3 + cytokine + MMP inhibitors	Reviewing the literature	Positive: Enhanced healing
Zhou et al.[113]	*In-vivo*	Rat	Acute full	rhFGF-18	Histologic analysis	Positive: Promoted chondrogenesis and promoted healing and regeneration
Sitcheran et al.[114]	*In-vivo*	Mouse	Acute full	TGF-β3	Histologic analysis	Negative: No improvement in healing
Gulotta et al.[115]	*In-vivo*	Rat	Acute and chronic full	TNF inhibitor	Histologic and biomechanical analyses	Positive: Elevated fibrocartilage, and enhanced load to failure and stiffness
Dorman et al.[117]	*In-vivo*	Mouse	Acute full	BMP-2–7	Histologic analysis	Positive: Fully healed enthesis without toxicity
Kabuto et al.[118]	*In-vivo*	Rat	Acute full	BMP-2–7	Histologic and biomechanical analyses	Positive: Improved biomechanical properties

Note: bFGF: basic fibroblast growth factor; BMP: bone morphogenetic protein; COMP: cartilage oligomeric matrix protein; CTGF: connective tissue growth factor; GF: growth factor; MMP: matrix metalloproteinase; MRI: magnetic resonance imaging; PDGF: platelet derived growth factor; rhFGF: recombinant human fibroblast growth factor; TGF: transforming growth factor; TNF: tumour necrosis factor; VEGF: vascular endothelial growth factor.

Scaffolds and augments

Augmentations via ECM or synthetic materials could potentially optimise RC enthesis healing.[120] Allografts, synthetic polymers, autografts, and xenografts have been used for RC repairs.[121] Despite improvements in xenografts and allografts decellularisation procedures, they still carry the risk of infection and inflammatory responses from residual donor DNA, high degradation rates, inferior mechanical qualities, and non-specific induction abilities.[43] These concerns have sparked an interest to create grafts and scaffolds for enhanced repairs. Engineered scaffolds with a mix of natural and synthetic biomaterials offer an alternative solution to combat adverse effects caused by synthetic materials. Natural biomaterials including fibrin, collagen, elastin, and hyaluronic acid offer extracellular signals that facilitate cell infiltration and tissue regeneration, where positive results with good host tissue integration, remodelling, and improvement in biomechanical qualities are reported in animal trials employing them.[122, 123]

Known to selectively differentiate BMSCs to chondrocytes, and gelatin methacrylol, a novel biomaterial with promising results in drug carrying, enhanced healing. kartogenin-loaded gelatin methacrylol hydrogel scaffold with bone marrow stimulation promoted fibrocartilage formation and resulted in superior mechanical properties in acute full RC repairs.[124] Compared to traditional double row suture repairs, engineered tissue grafts with 6 months follow-up showed 11% increased elastic modulus, the repaired enthesis was formed similarly to the native tissue, suggesting potential long-term retear prevention.[93]

Exosome-delivered BMP-2 and polyaspartic acid in an acute full RC tear rabbit model resulted in increased tissue mineral density and ultimate load strength, via Smad/RUNX2 signaling pathway. Additionally, tendon regeneration- and cartilage differentiation-related expressions were upregulated, suggesting the positive potential of using bioactive scaffolds in enthesis healing.[125] Since stem cells contribute to healing by autocrine/paracrine signaling through GFs and cytokines, delivering GFs via scaffolds is a simpler and more direct approach to improve RC healing. While interleukin-1 beta inhibited chondrogenesis and maturation of MSCs, the mechanical functionality of the tissue was preserved with three-dimensional (3D) woven polycaprolactone scaffolds.[126] Highlighting the importance of developing strategies to protect against the deleterious effects of cytokines.

A novel strategy combined a 3D printed polylactide-co-glycolide acid scaffold with a cell-laden collagen hydrogel to fabricate layered structures. Mechanical properties improved supporting growth, proliferation, tenogenic differentiation of human ADSCs, and excellent biocompatibility.[127]

As for clinical studies, long-term effect of a polypropylene patch was assessed on large chronic RC repairs and compared with collagen patches, in a patient cohort of 66-year-old. Results showed superior outcomes in muscle strength, pain score, and tendon integrity via ultrasound after a 3-year follow-up.[128] Repairs augmented with 3D biological collagen-I mesh in moderate and large RC tears of patients over 50 years, followed-up for 24-month resulted in better arranged collagen fibres, inflammatory cells less infiltrated, and lower RC retears at 17%.[129]

Although revealed to lower re-ruptures and tissue oedema in animals, porcine small intestine submucosa has been shown ineffective in humans.[130, 131] Due to poor functional results and significant complications, trials cautioned against using small intestine submucosa for RC repairs.[131, 132]

In general, scaffolds provide a growth microenvironment for cells and can be used as carriers for seeded cells and GFs, creating optimal conditions for RC enthesis healing. However, those technologies are still tackling the formation of fibrous cartilage, inflammatory reactions, elevated degeneration rates of the grafted scaffolds, and long-term follow-up.

Demineralised bone matrix

Demineralised bone matrix (DBM) is cancellous bone with osteoinductive and osteoconductive characteristics, known to elicit good adhesion, proliferation, and differentiation of MSCs.[133] DBM-based repairs have not been consistent in improving collagen organisation and fibrocartilage formation, nor result in higher bone mineral density.[134] However, supplementing them with BMSCs resulted in superior outcomes in chronic full tears.[135] Additionally, the use of DBM-based sponge hydrated with PRP resulted improved strength and histological structure in chronic full tears.[136] Despite this, when evaluating the clinical outcomes of patients undergoing biologically enhanced DBM-augmented RC repairs, 50% of patients' magnetic resonance imaging (MRI) confirmed supraspinatus failure.[137]

A more recent study fabricated a gradient multi-tissue construct that mimics structural, compositional, and cellular heterogeneity of the native enthesis designed by 3D cell-printing and tissue-specific decellularised ECM bioinks, where findings suggested improvement in restoring shoulder function.[138] The first human pilot study was performed to assess the safety and efficacy of autologous dermal fibroblast (ADF) injections on full chronic RC repairs of patients aged 20–80 years. Fibroblast samples were obtained from the patients' gluteal region and cultured for four weeks. Patients from both, the control group who did not have an ADF injection, and experimental group, underwent standardised post-operative rehabilitation program involving ice application for 5 days and tramadol for a week, alongside abduction brace immobilisation for five weeks. Exercises such as shoulder shrug and active elbow and forearm range of motion were encouraged immediately after surgery. 10–12 weeks after surgery active-assisted, active range of motion, and strengthening exercises were performed, with return to sport allowed after 6 months. Successful healing without adverse effects was reported in 1-year follow-up.[139] However, this study was limited by the small number of participants and the optimal dosage of ADF was not established. It is difficult to conclude the effectiveness of DBM-based augments on the overall healing process. Larger studies are necessary to examine its true effectiveness and long-term effect.

Platelet-rich plasma

PRP provides a rich source of GFs and cytokines such as PDGF, TGF-β, FGF, VEGF, and IGF.[140] In a study comparing the clinical and structural outcomes between arthroscopic repair of full thickness RC tears with and without PRP supplementation, retear rates were lower with PRP in tears greater than 3 cm, with improved Constant score.[141] Conversely, platelet-rich fibrin clot matrix, a variant of PRP with a fibrin matrix showed no difference in tendon thickness and greater tuberosity coverage in chronic full tears, and positive outcomes in partial tears.[142] However, this could be due to variable PRP preparation used, the nature of PRP used, and level of platelet activation not being accounted.[143] Thus, future research should focus on controlled PRP formulations to judge the benefits of this intervention more accurately.

Systematic reviews revealed PRP injections intraoperatively to produce better long-term pain and shoulder function outcomes following repairs in chronic full tears. While for

short-term follow-ups, PRP was superior in improving function only, in partial RC tears.[144-147] Post-operative subacromial PRP injections on patients with partial RC tears revealed improvement in functional outcomes up to 6 months, despite magnetic resonance imaging structural outcomes being insignificant, and long-term follow-up not being recorded.[148] Moreover, PRP combined with sodium hyaluronate yielded better outcomes in partial RC tears in younger population after 12 months of follow-up.[149] Recent meta-analyses showed PRP augments with double-row constructs have the best outcomes for chronic full tears, according to visual analogue scale (VAS), Constant, Simple Shoulder Test and retears.[150, 151]

Ilhanli et al.[152] debated that PRP may be as effective as physiotherapy interventions in patients with chronic partial tears followed up for 12 months. Despite a study showing an increase in PRP concentration after exercise, it remains unknown whether physiotherapy could enhance the effect of PRP.[153] Moreover, the literature varies in terms of exercise type, intensity, and duration for RC tears.[154] Standard rehabilitation protocols and ideal platelet concentrations for PRP augmented repairs are essential to preserve outcomes and create tailored care for patients with different backgrounds and abilities.

PRP is considered a suitable alternative to corticosteroid injections, which are commonly used clinically to manage RC tears. Achieving pain relief and good clinical outcomes add to the benefit of avoiding the adverse effects of corticosteroids on the body, which makes it an alternative approach to managing symptomatic RC tears, in both; young and athletic, and older populations with comorbidities. **Table 4** summarises the findings.

Table 4. Summary of scaffold-based therapies literature findings

Author	Study	Model	Tear	Intervention	Outcome measure	Study results
Huang et al.[124]	*In-vivo*	Rabbit	Acute full	KGN-loaded GelMA hydrogel + BMSC scaffold	Macroscopy, microcomputed tomography, histology, and biomechanical tests	Positive: Promoted fibrocartilage formation and superior mechanical properties
Novakova et al.[93]	*In-vivo*	Sheep	Acute full	Engineered tendon construct with BMSCs	X-ray and biomechanical tests	Positive: Native-like enthesis with higher modulus
Han et al.[125]	*In-vivo*	Rabbit	Acute full	BMP-2 + polyaspartic acid + Smad/RUNX2 signaling	Transmission electron microscopy staining; Biomechanics and histological assessment	Positive: Increased bone and tissue mineral density and ultimate load strength
Ousema et al.[126]	*In-vitro*	RC tear		3D woven PCL scaffold + IL-1 inhibition on MSCs	Histological, biomechanical, and immunohistochemistry analyses	Positive: Mechanical functionality preserved with the use of a 3D woven PCL scaffold
Jiang et al.[127]	*In-vitro*	RC tear		3D PLGA scaffold + a cell-laden collagen hydrogel + ADSCs	Histological and biomechanics analyses	Positive: Improvement in mechanical properties and biocompatibility
Iannotti et al.[131]	Clinical	Human	Chronic full	SIS	Penn shoulder-score questionnaire and MRI	Negative: No improvement in healing and clinical results
Malcarney et al.[132]	Clinical	Human	Chronic full	SIS	Study discontinued due to adverse effects	Negative: Inflammatory reaction
Sclamberg et al.[130]	Clinical	Human	Chronic full	SIS	Patient questionnaire, MRI, and ASES	Negative: No improvement and worse pot-operative outcomes
Ciampi et al.[128]	Clinical	Aging human	Chronic full	Polypropylene augmentation patch	Ultrasound, muscle strength, and VAS	Positive: Improved muscle strength, pain score, and tendon integrity
Cai et al.[129]	Clinical	Aging human	Chronic full	3D biological collagen-I mesh	MRI, VAS, UCLA SST, and Constant score	Positive: Less retear rates
Hoberman et al.[133]	*In-vitro*	RC tear		DBM + BMSCs + PRP	Adhesion, proliferation, and differentiation assays	Positive: Better adhesion, proliferation, and differentiation
Thangarajah et al.[134]	*In-vivo*	Rat	Chronic full	DBM	Histological analysis	Negative: No improvement in collagen organisation and fibrocartilage formation
Thangarajah et al.[135]	*In-vivo*	Rat	Chronic full	DBM + MSCs	Histological analysis	Positive: Enhanced healing

Table 4. Continued

Author	Study	Model	Tear	Intervention	Outcome measure	Study results
Smith et al.[136]	*In-vivo*	Canine	Chronic full	PRP + DBM	Histological and biomechanical analysis	Positive: Improvement in strength and histological structure
Wellington et al.[137]	Clinical	Human	Chronic full	DBM + MSCs	MRI	Negative: Supraspinatus failure
Chae et al.[138]	*In-vivo*	Mouse	Chronic full	3D cell-printed tendon-bone interface construct	Gait analysis, histological and biomechanical analysis	Positive: Fully formed enthesis, improved shoulder outcome and biomechanical properties
Yoon et al.[139]	Clinical	Aging and young human	Chronic full	ADF	ROM, VAS, and MRI	Positive: No adverse effects, improved VAS, and functional scores
Warth et al.[141]	Clinical	Human	Chronic full	PRP	MRI and Constant score	Positive: Lower retear and improved constant score
Castricini et al.[142]	Clinical	Human	Chronic partial	Autologous PRFM	MRI	Positive: Improved tendon integrity
			Chronic full	Autologous PRFM	MRI	Negative: No difference in constant score and tendon integrity
Giovannetti de Sanctis et al.[144]	Systematic review	Human	Chronic partial	PRP	Shoulder function and VAS	Positive: Improved pain and shoulder function
Von Wehren et al.[145]	Clinical	Human	Chronic partial	PRP	MRI, Constant score, ASES, shoulder ROM, and VAS	Positive: Improved pain and function
Xu and Xue[146]	Systematic review	Human	Chronic full	PRP	Retear rate, Constant, UCLA, ASES, VAS, and adverse effects	Positive: Improved shoulder outcome and reduced retear rate
Rha et al.[147]	Clinical	Human	Chronic partial	PRP	Shoulder Pain and Disability Index, ROM, and ultrasound	Positive: No adverse effects, and improved shoulder pain and function
Shams et al.[148]	Clinical	Human	Chronic partial	PRP	MRI, ASES, Constant Score, SST, and VAS	Positive: Improved shoulder function and minor MRI improvement
Cai et al.[149]	Clinical	Young human	Acute partial	SH + PRP	VAS, Constant score, and MRI	Positive: Better VAS, constant score, and MRI findings
Ryan et al.[150]	Systematic review	Human	Chronic full	PRP	Constant, ASES, UCLA, SST, VAS, and retear rate	Positive: Reduced retear rates and improved clinical outcomes
Lavoie-Gagne et al.[151]	Systematic review and meta-analysis	Human	Chronic full	PRP	Clinical characteristics, retear rates, ROM, and patient reported outcomes	Positive: Reduced retear rates and improved clinical outcomes
Ilhanli et al.[152]	Clinical	Human	Chronic partial	PRP	ROM, VAS, Disabilities of Arm, Shoulder and Hand questionnaire, Neer's, Hawkins' and drop arm tests and Beck Depression Inventory questionnaire	Negative: Results were not superior to physiotherapy

Note: 3D: three-dimensional; ADF: autologous dermal fibroblast; ADSC: adipose-derived stem cell; ASES: American Shoulder and Elbow Surgeons; BMP-2: bone morphogenetic protein-2; BMSC: bone marrow mesenchymal stem cell; DBM: demineralised bone matrix; GelMA: gelatin methacrylol; IL-1: interleukin-1; KGN: kartogenin; MRI: magnetic resonance imaging; PCL: polycaprolactone; PLGA: polylactide-co-glycolide acid; PRFM: platelet-rich fibrin clot matrix; PRP: platelet-rich plasma; RC: rotator cuff; ROM: range of motion; SH: sodium hyaluronate; SIS: small intestine submucosa; SST: Simple Shoulder Test; UCLA: University of California Los Angeles; VAS: visual analogue scale.

Biomechanical Loading Response

Loading tendons is critical for the maintenance of developing entheses, and tissue deformity, delayed mineralisation, and porous non-mineralised tissues are observed when unloaded. Mechanical stimulation increases TGF-β1 and Prrx1$^+$ cells to stimulate enthesis repair.[155] Unloading affects chondrocyte hypertrophy, leading to fibrocartilage absence at the insertion by eight weeks of immobilisation.[36] Reduced humeral volume with flatter surface and morphological changes comparable to those with cerebral palsy were noted, which is attributed to an increase in osteoclasts activity. Hence, blocking osteoclasts activity by bisphosphonate drugs partially recovers bone mineralisation and volume.[36, 37] This imbalance, therefore, contributes to developing an overall mechanically inferior tissue.

While prolonged and immediate mechanical loading induced adverse effects, low-intensity loading was beneficial as opposed to complete removal.[156-158] Since immediate excessive and prolonged loading produce adverse effects, and removal causes malformation, a requirement for balance between loading and healing is essential. When compared to various rehabilitative regimens, simple progressive loading is ideal.[159]

Discussion

RC tears are one of the most common causes of pain and dysfunctions in the shoulders, occurring in 9% under the age of 20 years to 62% until 80 years old.[160] Overhead-sport athletes are at higher risk of chronic RC injuries, due to repetitive loads leading to microtraumas, while contact-sport athletes have a higher risk of traumatic acute tears.[161] As for the aging population, degenerative pathologies are the most prevalent mechanism of injury.[162] Older patients with chronic tears would benefit from non-operative approaches, and younger athletes presenting acute tears require surgery, due to expectations of returning to competition. However, competitive athletes record lower return rates compared to recreational ones.[163] The reason for this remains multifactorial and may not be directly related to the repair, but rather a result of psychological factors such as fear of injury reoccurrence.[164, 165]

RC repairs present good short-term pain and function improvement, and high retears in the long-term.[166] Failure of complete healing urges the shift to alternative strategies aiming at restoring the native tissue's structure and biomechanical properties. Since the RC enthesis is made of a variety of cellular components organised in a gradient complex ECM structure, its regeneration requires the co-regulation of multiple factors.[167]

Stem cell role

The effectiveness of using stem cells to promote RC enthesis healing lies in regulating the differentiation of stem cells into target cells. This regulation is affected by certain factors: (1) the interaction between cells, (2) GFs and signaling molecules in promoting their expression, and (3) local microenvironment and mechanical stimulation. Obtaining stem cells and their survival rate are issues faced when used for RC enthesis healing, hence, improving this can broaden their use in hypoxic conditions. Additionally, methods in which stem cells are taken from patients can reduce patient inconvenience.[167]

Growth factor role

GFs regulate RC enthesis healing in several ways: (1) different GFs are expressed in stages of healing, with GFs promoting angiogenesis present in the inflammatory stage, and those endorsing cell differentiation for collagen synthesis at the repair and remodelling stages.[168] (2) As a signaling molecule, by promoting the expression of genes and proteins related to regulate the biological behavior of cells. (3) By interacting with other GFs. It is essential to consider that: (1) GFs have a short half-life, thus carriers to delay their local release rate and maintain their effect are essential. (2) GFs have different effects based on the tear type. (3) The role of some GFs and their signaling pathways remains unclear. Considerable variations persist between studies in the preparation of GFs (recombinant, synthetic), delivery methods (local injections, systemic, within scaffold, coated sutures), and timing (pre-, peri-, post-operative, and repeated dosages).

Scaffold's role

The choice of scaffold material should meet the growing needs of specific cells, simulate its ECM, mechanically support, and provide a suitable growth environment. Since the main component at the RC insertion is collagen, the application of biomaterials with collagen matrix as the main component is the most effective.[92, 129] Patches designs are essential to assure its proper interaction with the microenvironment for proliferation, adhesion, differentiation, and morphology.[169-172]

Summarised outcomes

Findings suggested a lack of single optimal strategy for restoring RC enthesis. Mechanical stimulation is necessary; its absence cause detrimental effects, and long-term progressive loading rehabilitation aids in achieving a comprehensive RC repair.[16, 36, 37, 155, 157, 159]

Augmenting MSCs with adenoviral MT1-MMP had positive biomechanical outcomes in acute full tears[75] (**Figure 2**). ADSCs present contradicting outcomes in acute and chronic full tears, and BMSCs were recorded as negative in acute.[73, 77, 80, 81] However infusing BMSCs with PRP and imbedding ADSCs in fibrin sealant scaffold enhance repairs.[72, 78] Conversely, TGF-β3-supplemented ADSCs did not enhance acute full tear healing.[80] For chronic full ones, MSCs combined with hyaluronic acid, BMSCs with repeated channeling, and ADSC sheets interposed improved outcomes.[68, 69, 79] Clinical trials in chronic partial tears with BMSC-enhanced augmentation improved healing and prevented retears.[70, 71]

For signaling molecules, systemic PTH produced positive outcomes in full acute and chronic tears.[87-89] Ihh with MSCs had positive outcomes in acute partial and full tears.[29, 82, 83] BMP-12–14, basic fibroblast growth factor, COMP, connective tissue growth factor, PDGFB, BMP-2–7, recombinant human FGF-18, TGF-β1, and the combination of BMP and VEGF resulted positively, while TGF-β3 remained ineffective in acute full tears.[43, 105-107, 110, 113, 114, 117, 118] Inhibiting TGF-β1 was effective in acute full tears, and TNF inhibition was better in full acute and chronic tears.[112, 115] Most promising outcomes were attained by combining TGF-β3 with a cytokine and MMP inhibitor in acute partial and full tears.[32]

Acute – Full	Chronic – Full	Chronic – Partial	Chronic – full – age	*In-vitro*	Acute – Partial	Acute – Partial –Young	Chronic – full – Young
BMP-12-14[104, 105]	ADSC + suture[76]	Autologous PRFM (Human)[140]	ADF (Human)[137]	DBM + BMSCs + PRP[131]	TGF-β + cytokine + MMP inhibitors[32]	SH + PRP (Human)[147]	ADF (Human)[137]
bFGF[104, 105]	MSC + HA[172]	BMSC[59, 70]	3D biological collagen-I mesh[127]	3D PLGA scaffold + a cell-laden collagen hydrogel + ADSCs[125]	Ihh[29, 81]		
COMP[104, 105]	PRP + DBM[134]	PRP[142, 143, 145, 146]	Polypropylene[126]	3D woven PCL scaffold + IL-1 inhibition on MSCs[124]			
CTGF[104, 105]	ADSC sheets interposed at the enthesis[77]	PRP (Human)[150]					
PDGFB[104, 105]	ADSC[78, 79]						
TGF-β1[104, 105]	DBM + MSCs[133]						
BMP and VEGF[43, 106]	PRP (Human)[139, 144, 148, 149]						
BMP-2 + polyaspartic acid + Smad/RUNX2 signaling[124]	Controlled systemic PTH injections[87]						
Inhibiting TGF-β1[111]	TNF inhibitor[113]						
PRP-infused BMSC[124]	3D cell-printed tendon-bone interface construct[136]						
TGF-β3 + cytokine + MMP inhibitors[32]	BMSC with repeated channeling[68]						
TNF inhibitor[114]	ADSC[78]						
Systemic PTH injections[86,87]	SIS[128-130]						
Engineered tendon construct with BMSCs[92]	DBM[132]						
BMP2-7[116, 117]	DBM + MSCs (Human)[135]						
Ihh[81]	Autologous PRFM (Human)[140]						
MSC + Ihh[81]							
ADSC imbedded in fibrin sealant scaffold[77]							
rhFGF-18[112]							
MT1-MMP-transduced MSCs[74]							
KGN-loaded GelMA hydrogel + BMSCs scaffold[123]							
BMSC[72]							
ADSC[79,80]							
ADSC + TGF-β3[79]							
TGF-β3[107, 109, 113]							

Figure 2. Categorised literature findings: stem cells, GFs, and scaffolds vary in effect depending on the extent of the tear, chronicity level, population, and their combinations. Majority of studies investigated acute full tears, while less studies were investigating partial and full chronic tears. Very few studies considered the age of the studied population. 3D: three-dimensional; ADF: autologous dermal fibroblast; ADSC: adipose-derived stem cell; bFGF: basic fibroblast growth factor; BMP: bone morphogenetic protein; BMSC: bone marrow mesenchymal stem cell; COMP: cartilage oligomeric matrix protein; CTGF: connective tissue growth factor; DBM: demineralised bone matrix; GelMA: gelatin methacrylol; GF: growth factor; HA: hyaluronic acid; Ihh: Indian hedgehog; KGN: kartogenin; MMP: matrix metalloproteinase; MSC: mesenchymal stem cell; PCL: polycaprolactone; PDGFB: platelet-derived growth factor-B; PLGA: polylactide-co-glycolide acid; PRFM: platelet-rich fibrin clot matrix; PRP: platelet-rich plasma; PTH: parathyroid hormone; SH: sodium hyaluronate; SIS: small intestine submucosa; TGF: transforming growth factor; TNF: tumour necrosis factor.

Outcomes from scaffold-based studies are promising and reached clinical trials. Polypropylene augmentation patch resulted in good outcomes in aging models with chronic full tears.[128] 3D cell-printed tendon-bone interface construct revealed positive outcomes in chronic full tears contrasting small intestine submucosa.[130-132,138] Kartogenin-loaded gelatin methacrylol with BMSCs, engineered constructs with BMSCs, and BMP-2 with polyaspartic acid and Smad/RUNX2 improved acute full tears.[93, 124, 125] DBM-based scaffold was not beneficial, however, augmenting it with MSCs and PRP in separate animal models was effective.[134-136] Clinical trials on DBM and MSCs combination did not replicate similar outcomes.[137] This could be attributed to the varied forms of scaffold materials, since animal models have shown promising results with strips of cancellous DBM, while clinical studies used sponges. Sponges can be displaced from the interface site, whereas strips and patches can be more securely sutured into the interface.

Autologous platelet-rich fibrin clot matrix clinical studies were more beneficial in chronic partial than full tears.[142] ADF was safe and effective in younger and older populations with chronic full tears.[139] While PRP is proven beneficial in chronic partial and full tears, it wasn't superior to physiotherapy.[126, 141, 144-148, 150-152] Sodium hyaluronate combined PRP was effective in acute and partial tears of younger populations.[149] 3D collagen I mesh augmentation in older populations with chronic full tears resulted in positive long-term outcomes.[129] Novel multifactorial lab-based tissue engineering strategies such as 3D-woven polycaprolactone scaffold with IL-1 inhibition on MSCs, 3D polylactide-co-glycolide acid scaffold in cell-laden collagen hydrogel and ADSCs, BMSCs and PRP enhanced DBM-based scaffold had promising outcomes.[126, 127, 133]

Potential reasons for variations

Outcomes vary since there is no standardised controlled environment prior and after repairs. They differ in methodologies, animal models, and mechanical follow-ups; some allow free mobilisation after repairs, while others impose treadmill walking regimens or restrict movement.

It is difficult to determine if variations are due to the interventions, animal models, mechanical environment, or extent and mechanism of tears. Some studies created acute dissection or detachment, immediately injecting it with the examined substances prior to repairs. However, that does not represent the clinical acute and chronic mechanism of tear, as it does not allow time for the inflammatory process to take place; no blood supply restriction, enthesis degeneration, and fatty infiltration. Other studies subject animals to a treadmill regimen prior to the intervention to exhaust tendons and replicate overuse. Findings should be similar in both scenarios, to indicate that the intervention has a definitive outcome.[173] Treadmill regimen does not ideally replicate injury process in athletes performing sports since childhood. Professionally trained athletes have a lower risk of RC injury compared to amateurs that lack proper loading techniques, healthy balanced diet, sleep routine, and psychological well-being. This might fit amateur athletes scenario who are exposed to improper unconditioned loading. Additionally, small animal models such as rats and rodents have a far better healing capacity than larger animals and humans. Their measures of success should not be solely determined based on morphology, but also the timeframe and long-term effects. Surgical techniques used also affect the outcome of biological therapies. Introducing stem cells via tunnels produced superior outcomes to surface repairs. Additionally, biomaterial patch that covered the repair addressed MSCs long-term survival.[174-176]

Clinical outcomes are affected by patients' occupation, demographics, age, gender, comorbidities, and tear mechanism and extent. Moreover, patient outcome measures have a degree of subjectivity, affected by expectations and psychosocial well-being.

Conclusion

To take research of tendon-bone enthesis for RC tears forward, there are critical factors involved in the healing of the enthesis, which is supported by what has been presented and rationale for, where without them there wouldn't be a successful healing. Tissue engineering has promising outcomes in achieving the complex RC enthesis structure and function. Different cells and GFs at specific times and environmental control can maximise the restoration of the native enthesis. Despite the positive outcomes of tissue engineering strategies, progressive loading environment is essential for optimum healing. Although the effects of the discussed interventions have mostly been confirmed in animal experiments, the intrinsic connections between cells at the interface and the molecular signaling pathways involved in tissue repair and regeneration still need to be further explored in humans. Nevertheless, the limitations mentioned are important to be considered for future studies to be applied in clinical practice.

This paper described the microscopic anatomy of the healthy RC enthesis, its role in facilitating force transmission, and the biomechanical adaptations. It then discussed the structural changes that accompany injured RC enthesis and the factors influencing its healing potential. Positive outcomes in the field of stem cells, GFs, and scaffolds along with their challenges, limitations, and variety of implementation are explained. The results support the proposed hypothesis that interventions should be tailored according to the tear extent, chronicity, and population studied.

Study limitations

Inconsistencies in reported outcomes derive from variations in patients' occupation, demographics, age, gender, comorbidities, and tear mechanism and extent. Moreover, patient reported outcome measures are subjective, and influenced by expectations and psychosocial well-being. Perspective studies would benefit from addressing the following:

1. The difficulties in advancing *in vivo* studies to clinical trials and the regulatory constraints associated with utilising biological interventions which have proven successful in the former, to the latter.
2. Biological materials availability and manufacturing in forms that can be utilised clinically in RC repair.
3. The potential for personalised biological intervention materials.
4. Solutions for aging patients and professional athletes requiring 100% recovery to return to competition.
5. Influential medical, environmental, social, and psychological factors.

Author contributions

Both authors contributed to the design, literature research, analysis, and preparation of the manuscript. Both authors revised the manuscript and approved the final version of the manuscript.

Financial support

None.

Acknowledgement

Ahlam A. Abdalla would like to extend my gratitude to Dr. Catherine Pendegrass for encouraging and supporting me throughout. We appreciate UCL for providing the resources and easy access to the literature, as it was essential to obtain the requirements and complete this paper. This review was supported by the United Arab Emirates Ministry of Education, and University College London.

Conflicts of interest statement

Both authors declare that they have no competing interests.

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Received: February 4, 2023
Revised: March 15, 2023
Accepted: May 5, 2023
Available online: June 28, 2023