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Regenerative medicine in shoulder injuries: Stem cell augmentation and multi-tissue rotator cuff repair

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Abstract

Shoulder injuries, such as rotator cuff tears (RCTs), SLAP lesions, tendinopathy, and dislocations, are prevalent among athletes and often result in prolonged recovery, decreased range of motion, and reduced career longevity. The evolving field of regenerative medicine, stem cell augmentation, and multi-tissue regeneration provides a promising pathway for improved recovery. Previous research has explored links between bone-tendon-muscle unit healing, retear rates, and recent innovations such as mesenchymal stem cells (MSCs), growth factors (GFs), platelet-rich plasma (PRP), and tissue-engineered scaffolds (TES). This paper presents a critical review of literature published from 2019 to 2025, assessing measurable outcomes including tendon healing, structural integrity, biomechanical performance, and retear rates. A total of 37 eligible studies were analysed after applying inclusion criteria that prioritised methodological transparency and clinical relevance. Findings suggest that regenerative augmentation can significantly improve repair outcomes, particularly in severe cases. In cases of severe or chronic injuries, combining traditional surgical techniques with regenerative medicine approaches may improve patient outcomes by enhancing tendon healing and reducing retear rates. However, variability in protocols and underpowered clinical trials limit broad clinical adoption. This review highlights the emerging role of MSCs, PRP, and TES in sports medicine and discusses current limitations and future directions for translational integration.

Keywords: *rotator cuff repair, regenerative medicine, mesenchymal stem cells, platelet-rich plasma, tissue-engineered scaffolds, sports injuries*

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1. Introduction

Rotator cuff injuries are among the most prevalent musculoskeletal disorders, commonly resulting in chronic shoulder pain, reduced range of motion (ROM), and high retear rates following surgical intervention (Dickinson & Wilson, 2019). These injuries represent a major cause of disability not only in the general population but also among athletes, where the physical demands on the shoulder joint are particularly high. The rotator cuff comprises four muscles, supraspinatus, infraspinatus, teres minor, and subscapularis, that play a critical role in stabilising the glenohumeral joint and facilitating dynamic shoulder movement. Together, these muscles enable abduction, rotation, and fine motor control of the shoulder, allowing for a wide range of motion while ensuring joint integrity and stability during strenuous activity (Maruvada et al., 2023).

In athletic populations, rotator cuff pathology has significant consequences that extend beyond physical discomfort. Injuries to this muscle group can impair performance by reducing strength and endurance, compromising ROM, and prolonging rehabilitation timelines. Even relatively minor injuries can disrupt training regimens, competitive participation, and long-term athletic career trajectories. Standard management approaches often begin with conservative treatment, but when symptoms persist or functional deficits become severe, surgical intervention is frequently pursued. Arthroscopic repair is one of the most commonly employed techniques, especially for partial- and full-thickness tears. While it has advantages such as minimally invasive access and quicker initial recovery, arthroscopy remains less effective in managing extensive tears or degenerative conditions of the rotator cuff (Dickinson & Wilson, 2019).

Limitations in surgical techniques have been highlighted in multiple studies, with high retear rates and incomplete tendon-to-bone healing representing major challenges. Such complications not only diminish the success rates of surgical interventions but also increase the likelihood of persistent pain and functional impairment. For athletes, these outcomes translate into prolonged absences from training and competition, reduced ability to return to previous levels of performance, and, in some cases, early retirement from sport. Beyond the physical effects, the psychological burden of re-injury and prolonged rehabilitation further complicates the recovery process, underscoring the need for more reliable and durable treatment options (Dickinson & Wilson, 2019).

The purpose of this paper is to conduct a comprehensive review of current literature on modern therapies in the treatment of rotator cuff injuries, with particular focus on athletic populations. Given the prevalence of such injuries across various sports disciplines, it is critical to evaluate both the short-term reliability and long-term efficacy of available therapies.

2. Literature Review

Regenerative medicine offers a promising alternative to conventional surgical techniques by employing biological approaches to repair damaged tissues and enhance functional recovery. Among these, mesenchymal stem cells (MSCs) have emerged as a particularly compelling option. MSCs are multipotent stromal cells with the unique ability to self-renew and differentiate into multiple cell lineages, including osteoblasts, chondrocytes, and tenocytes. These characteristics make them especially valuable for tendon regeneration, where structural integrity and biomechanical strength are essential. Beyond their differentiation capacity, MSCs exert pharmacological effects such as promoting angiogenesis, modulating immune responses, and stimulating tissue regeneration. These properties contribute to their growing appeal in translational research and clinical applications. Importantly, MSCs can be harvested from a wide variety of tissues, including bone marrow, dental pulp, umbilical cord, and adipose tissue, providing multiple accessible and viable sources for therapeutic use (Shan et al., 2024).

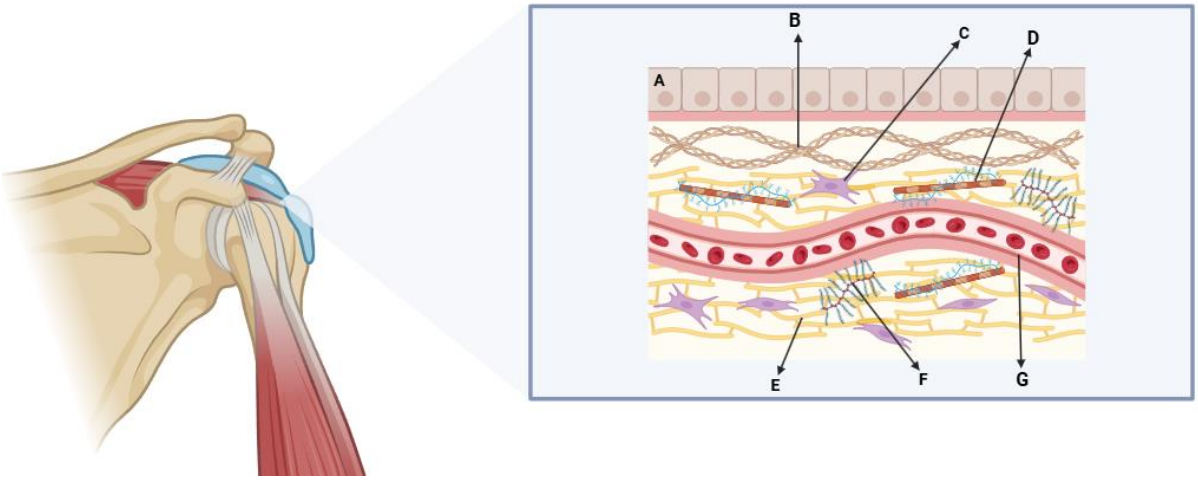
Another widely studied regenerative modality is platelet-rich plasma (PRP). PRP is an autologous concentrate derived from peripheral blood, enriched with platelets that release an array of growth factors (GFs), such as platelet-derived growth factor, transforming growth factor-β, vascular endothelial growth factor, and insulin-like growth factor-1. These bioactive molecules collectively support cellular proliferation, collagen synthesis, angiogenesis, and tissue remodeling, thereby accelerating the natural healing cascade at sites of injury (Egierska et al., 2023). In rotator cuff pathology, PRP therapy has been explored both as a stand-alone treatment and as an adjunct to surgical repair, with studies reporting mixed but encouraging outcomes in terms of pain relief, tendon healing, and reduced retear rates.

In addition to cellular and biologic therapies, tissue engineering strategies (TES) are increasingly being investigated as complementary tools in regenerative medicine. TES involve the development of biomaterial scaffolds designed to mimic the tendon’s extracellular matrix (ECM), which is primarily composed of structural proteins and polysaccharides that maintain

biomechanical strength and tissue homeostasis. By recreating this microenvironment, TES serve as platforms that facilitate cellular adhesion, proliferation, and differentiation, ultimately guiding tendon regeneration (see Figure 1). Advanced scaffold designs not only aim to replicate the physical properties of tendon tissue but also incorporate bioactive cues that promote cell-specific signaling and integration within host tissue (Lim et al., 2021). The combination of scaffolds with biologics, such as MSCs and PRP, has shown synergistic effects in preclinical studies, highlighting the potential of integrative regenerative strategies.

Figure 1

Cellular and matrix components of tendon ECM



Note: A magnified view of the tendon's ECM (ECM) reveals a complex microenvironment consisting of: (A) Tenocytes, (B) Type I Collagen Molecules (Triple Helix), (C) Tendon Stromal Cells (TSPCs), (D) type I collagen fibrils associated with proteoglycans, (E) Elastin Fibres, (F) Hyaluronic Acid Backbone with Attached Proteoglycan, and (G) Blood vessel (capillary). Together, these components contribute to the tendon's mechanical resilience, hydration, and regenerative potential. *Source:* Created with BioRender Software

The high incidence of rotator cuff pathology and the limitations of conventional interventions have prompted a surge of peer-reviewed investigations into regenerative approaches. Comparative studies evaluating MSC augmentation, PRP application, and scaffold-based TES against traditional techniques such as arthroscopic repair, tendon transfers, and open surgeries have demonstrated promising results. Outcomes assessed include tendon integrity, biomechanical strength, retear incidence, and sustained functional recovery. While early clinical and preclinical trials reveal encouraging improvements in healing potential and reductions in failure rates, significant challenges remain. Chief among these are inconsistent

treatment protocols, variability in patient response, and the current lack of long-term efficacy data across diverse athletic and non-athletic populations.

To address these gaps, this paper critically reviews the recent advancements in regenerative therapies for rotator cuff injuries, with a particular focus on their applicability to athletic populations. The discussion is structured as follows: Section 1 explores the biological and mechanical limitations of conventional rotator cuff repair, with emphasis on the high failure rates and retear risks associated with standard surgical methods. Section 2 reviews the molecular basis and therapeutic applications of PRP, while also considering the clinical inconsistencies that complicate its widespread adoption. Section 3 investigates the role of MSCs in tendon healing, comparing different tissue sources, assessing their translational readiness, and analysing their regenerative contributions. Section 4 examines TES, with particular attention to their integration with MSCs and PRP as part of a multimodal approach to enhance tendon repair and improve long-term functional outcomes.

Despite the promising findings of regenerative medicine, the path toward widespread clinical adoption requires addressing persistent obstacles, including standardisation of protocols, minimisation of patient variability in treatment response, and generation of robust long-term clinical data. Only by overcoming these challenges can regenerative strategies move from experimental therapies to reliable, evidence-based standards of care for athletes and the general population alike.

3. Methodology

This review examined clinical trials, meta-analyses, and preclinical animal studies that reported quantifiable outcomes in tendon healing, biomechanical integrity, retear incidence, and histopathological characteristics. Literature searches were conducted via Google Scholar and PubMed using keywords such as “rotator cuff repair,” “rotator cuff injury,” “stem cell regeneration,” “MSCs,” “PRP,” “biomaterial scaffolds,” “multi-tissue regeneration,” and “biologic augmentation.”

A total of 69 papers were reviewed and evaluated based on specific inclusion and exclusion criteria. The inclusion criteria required that studies be published between January 2019 and June 2025, peer-reviewed, and written in English. Eligible studies also had to involve regenerative interventions such as MSCs, PRP, or tissue-engineered scaffolds (TES), and report measurable outcomes or provide a mechanistic/biological rationale. These outcomes

included tendon integrity, retear rates, tissue degeneration, and healing cascades. Additionally, studies had to focus on rotator cuff and related shoulder pathologies. The exclusion criteria eliminated studies with insufficient methodological transparency, those lacking measurable clinical or preclinical outcomes, research focused on non-shoulder pathologies, and duplicate or non-peer-reviewed sources. Of the 69 papers selected for initial review, 32 were excluded based on these criteria.

4. Findings and Discussion

4.1. Current Challenges in Rotator Cuff Repair

Structural failure continues to be one of the major unresolved issues after rotator cuff repair. Key factors that inhibit healing and result in poor repair outcomes including: tear size (where a small tear is <1cm, a medium tear is 1-3cm, a large tear is 3-5cm, and a massive tear is >5cm [Ishigaki et al., 2021]), chronicity, patient age, muscle atrophy, and fatty infiltration (Zhang et al., 2022). Regenerative therapies are crucial for repairing the rotator cuff, as traditional surgical treatments often show high retear rates and limited long-term effectiveness (Dickinson & Wilson, 2019).

4.1.1. Impact of Fatty Degeneration and Infiltration on Repair Outcomes

Fatty degeneration refers to the progressive replacement of muscle fibres with adipose tissue, resulting in atrophy and impaired contractile function. This degeneration diminishes the muscles' ability to support the tendon during healing, leading to poor tendon healing outcomes (Bogdanov et al., 2021). Fatty infiltration is a closely related degenerative condition, causing damage to the tendon-muscle unit of the rotator cuff. It involves adipose deposition between myofibrils, which decreases tissue elasticity and compromises healing capacity (Yubran et al., 2024).

A preclinical rat study modelled chronic rotator cuff injury to evaluate the effects of persistent subacromial impingement on the supraspinatus tendon. Histological assessments, magnetic resonance imaging (MRI), behavioural testing, and gene expression profiling were utilised by the study to evaluate structural damage, including collagen disorganisation, tendon tearing, and fatty infiltration. After 8 weeks of treadmill running, the experimental group developed acromial bone hyperplasia, thickened cortical bone, bursal-side tendon tearing, collagen disorganisation, and partial fatty infiltration. Histology confirmed abundant

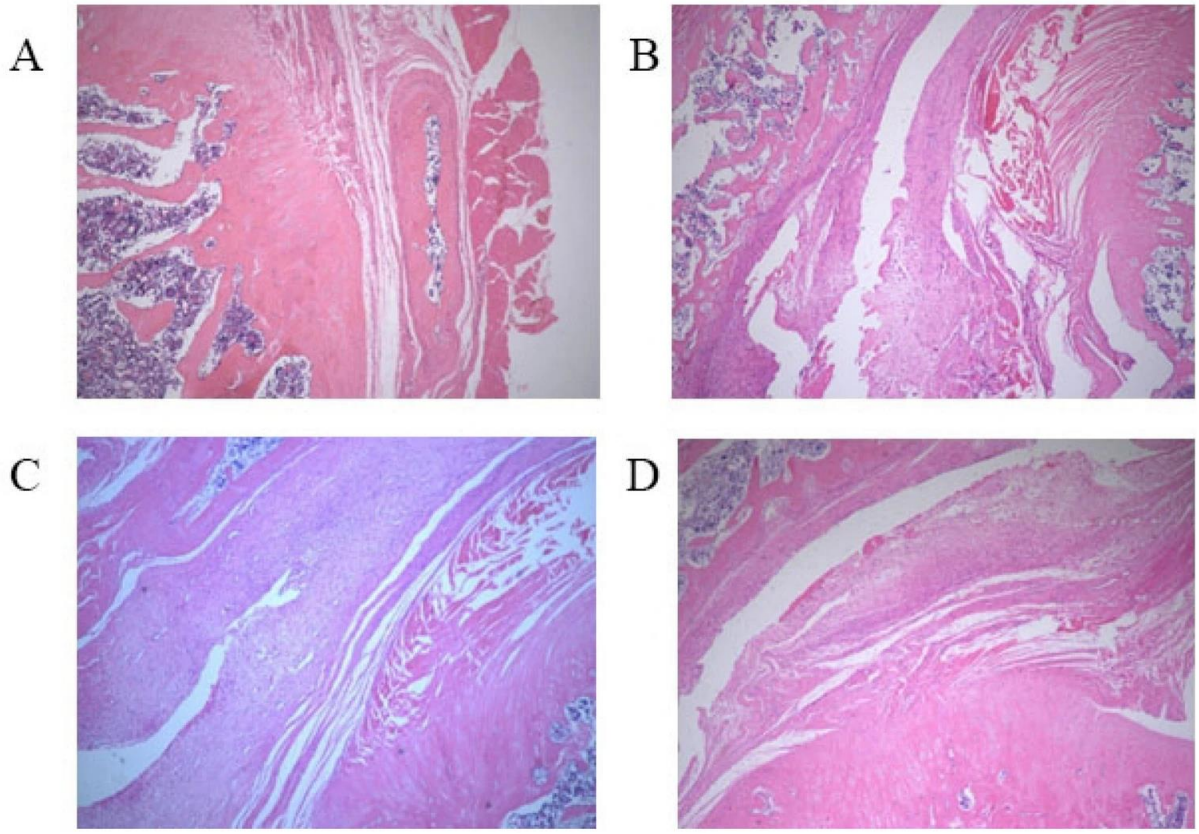
intramuscular adipocytes, indicating pronounced fatty infiltration in the muscle (Yuan et al., 2024). While this degeneration is recognised clinically as a factor linked to poor outcomes after rotator cuff repair, this study did not evaluate surgical treatment or healing capacity. Although the rat model provides insights to chronic rotator cuff injury progression and associated inflammatory gene expression, its anatomical and biomechanical differences from humans must be acknowledged. In humans, the rotator cuff is subjected to complex multidirectional loads during overhead sports and dynamic movements, forces that exceed the simplistic linear treadmill running used in rats. Moreover, the quadrupedal gait of rats differs substantially from the bipedal shoulder demands of human athletes, particularly in overhead throwing or contact sports.

Regarding the methodologies, the study included only 30 rats in each group, and while it used rigorous histological and MRI analysis, the small sample size and absence of quantitative measures of muscle atrophy and fatty infiltration (e.g., volumetric MRI, specific muscle area quantifications) limit the statistical power and generalisability of its findings. Moreover, rats exhibit higher intrinsic regenerative potential than humans, complicating the direct application of results to slower-healing athletic injuries. The use of a 3D-printed PolyEtherEtherKetone (PEEK) implant to induce impingement was innovative, but biomechanically distinct from overuse or acute traumatic mechanisms seen in athletes. The histological changes, such as collagen disorganisation and early fat infiltration, were clearly demonstrated in Figure 2. However, the lack of functional outcomes beyond gait analysis leaves unanswered questions about how such histological changes affect sport-relevant biomechanics.

Additionally, Matusuki et al. investigated fatty degeneration in rotator cuff muscles using MRI and transverse relaxation time (T2) mapping to provide quantitative measurements (Matsuki et al., 2024). In this study, 103 human patients were involved (52 males; 51 females) aged 42-83 years with varying degrees of rotator cuff damage, including partial (n=13), small (n=18), large (n=33), and massive (n=4) tears. Post-operative T2 values of the infraspinatus demonstrated a negative correlation with external rotation strength, suggesting that T2 mapping could serve as a marker of muscle strength. However, shoulders with retears did not show significant reductions in T2 values. As a result, significant improvements in ROM across all directions were observed, except for external rotation in the retear group.

Figure 2

Progressive rotator cuff degeneration on MRI



Notes: Representative sagittal T1-weighted MRI images illustrating rotator cuff muscle quality. (A) Aligned spindle-shaped fibroblasts and well-organised collagen; (B) By week 2, the chronic injury model shows disrupted, irregular collagen structure.; (C) At week 4, fat infiltration becomes apparent alongside tendon detachment; (D) By week 8, severe collagen disorganisation and visible fat interposition are observed at the bursal side, contrasting with relatively preserved collagen alignment on the humeral side (Yuan et al., 2024).

Furthermore, patients with intact shoulders demonstrated more substantial improvements in external rotation strength and significantly lower post-operative T2 values. Although the average change in T2 values for the infraspinatus in these patients was only 2.8 msec, the results suggest that this change holds clinical relevance, as the investigation is a reasonably powered study. These findings underscore that persistent or progressive fatty degeneration impairs functional recovery, particularly external rotation strength, and highlight a major limitation of traditional rotator cuff repair: it cannot reverse established fatty infiltration. This reinforces the importance of early surgical intervention and the need for strategies addressing both tendon reattachment and muscle quality to optimise outcomes. As a result, the follow-up rate was found to be 73%, which introduces selection bias, meaning that these patients may not truly be representative of the original patient population, thus

compromising the generalisability of the findings. Consequently, the observed T2 value changes may not fully reflect treatment efficacy or risk in a broader population, limiting their clinical relevance.

4.1.2. Persistent Challenges in Surgical Outcomes

Zhao et al. (2021) identified risk factors, such as age, body mass index, diabetes, tear length, tear width, tear size area, amount of retraction, and compromised tissue quality as key predictors of poor healing outcomes following surgical repair. These factors contribute to retear rates, highlighting the limitations of traditional surgical interventions. This is especially relevant in the context of sports injuries, where the mechanical demands placed on the shoulder can be extreme and highly variable. Additionally, the wide variation in athletic body types, conditioning levels, and sport-specific loading patterns means that a one-size-fits-all surgical approach often fails to account for individualised tendon stress and healing capacity. As a result, even anatomically successful repairs may not restore performance in athletes with larger frames, higher lean mass, or compromised soft tissue quality, which highlights the need for personalised treatment strategies that integrate biological, mechanical, and sport-specific factors (Migliorini et al., 2023).

4.1.3. Biological Limitations of Fendon Healing and Rationale for Regenerative Approaches

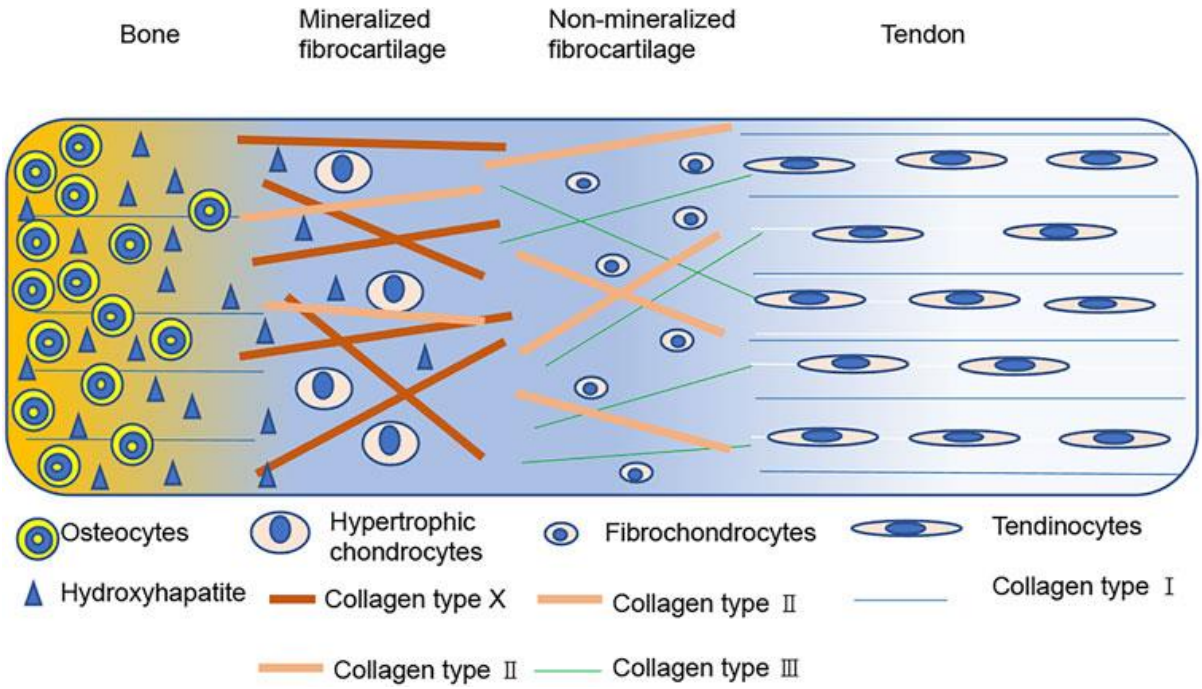
The limited biological capacity of tendons to regenerate after injury remains one of the core challenges behind these failures. Tendons are hypocellular and hypovascular, particularly at the tendon-bone interface (TBI), which restricts endogenous healing responses. In their systematic review, Bono et al. (2023) evaluated 40 studies: 29 preclinical (in vivo animal models) and 11 clinical. They concluded that while ~83% of preclinical studies reported positive biomechanical or histological effects, clinical evidence remains inconclusive due to variability. They emphasised the need for high-quality trials with standardised protocols to determine whether injectable biologics can reliably improve healing and reduce retears. While they identified promising biomaterials, ADSCs, and PRP, the majority of included studies were preclinical. Clinical trials were frequently limited by small sample sizes, heterogeneity in biologic preparation, inconsistent adherence to reporting standards, and level III evidence, weakening the translational strength of their conclusions.

Furthermore, the human trials varied significantly in design, intervention type, outcome measures, and follow-up duration, making meta-analysis infeasible. The review also highlighted the lack of standardised outcome measures and limited long-term data, constraining its utility for clinical decision-making. Thus, while the review supports the rationale that limited intrinsic tendon biology contributes to repair failure, its evidence base remains insufficient to guide widespread clinical adoption.

Despite advances in surgical techniques, conventional repairs still fall short of re-establishing optimal load transfer and long-term durability, as they fail to recreate the zonal transitions of the TBI, as shown in Figure 3. Emerging regenerative approaches, such as PRP, show promise in biologically augmenting tendon repair by addressing the limitations of poor tissue quality and high failure rates.

Figure 3

Structural transitions at the tendon-bone interface



***Notes**:* Diagram of the TBI showing the gradual transition from bone (osteocytes and hydroxyapatite), through zones of mineralised and non-mineralised fibrocartilage (containing hypertrophic chondrocytes and fibrochondrocytes in a collagenous matrix: types X, II, and III), to tendon tissue, composed mainly of aligned tenocytes and collagen type I fibres (Xu et al., 2022).

4.2. PRP: Applications and Challenges

4.2.1. Human Clinical Studies on PRP for Rotator Cuff Repair

A systematic review of meta-analyses conducted by Ahmad et al. (2022) involved studies reporting clinical outcomes of PRP augmentation in patients undergoing surgical repair of RCTs. Each meta-analysis included in the review was assessed for quality using the PRISMA checklist and the Oxman–Guyatt score. The studies under review included 13 meta-analyses, made up of data from a total of 1800 patients with follow-up times ranging from 12 to 36 months. The larger dataset gathered provides greater statistical power and a more generalisable understanding of PRP's clinical effects. Regarding PRP, a lower number of retears, improved short-term postoperative scores, and functional outcome was observed. Overall, the data reflects an increased understanding of PRP augmentation in arthroscopic rotator cuff repair. While early studies reported minimal clinical or radiological benefit, more recent, methodologically robust meta-analyses suggest PRP may reduce retear rates, enhance short-term outcomes, and improve functional recovery, indicating a potential shift in its clinical value. However, PRP is currently a heterogeneous intervention, with differences in preparation and delivery contributing to inconsistent results across studies. Consequently, its specific role in athletic populations is still unclear (Hamid & Sazlina, 2021).

4.2.2. Future Directions: Standardisation and Emerging Therapies

PRP remains a biologically plausible adjunct to rotator cuff repair, supported by its autologous origin and growth factor profile. However, methodological inconsistencies (particularly in preparation, activation, and delivery) continue to hinder reliable clinical translation. The current body of evidence highlights the need for high-quality, standardised trials that use clearly defined PRP protocols and clinically relevant endpoints. This is especially crucial in athletic populations, where treatment goals involve structural healing, rapid return to play, sustained performance, and minimal re-injury risk.

Although PRP leverages intrinsic growth factors and shows promise in selected contexts, inconsistent efficacy has shifted research toward complementary and alternative strategies (Collins et al., 2021). These include MSC therapies and scaffold-based approaches, which may not only enhance tendon repair but also restore tendon–bone integration and address neuromuscular recovery, features that are critical for athletic performance and long-term shoulder function.

4.3. MSCs: Beyond Tendon Healing

4.3.1. MSCs for Nerve Repair in Rotator Cuff Injuries

In preclinical models, MSC delivery, via injection or scaffold seeding, improved tendon structure, vascularity, and biomechanical integrity (Lavorato et al., 2021). Chronic rotator cuff injuries may also involve the brachial plexus, a complex nerve network originating from the cervical (C5 - C8) and upper thoracic nerve network (T1) that innervates the shoulder, arm, and hand. Damage to or irritation of the brachial plexus can lead to additional symptoms, such as neuropathic pain, muscle weakness, and sensory deficits in the upper limb (Li et al., 2023).

Recent work by Lavorato et al. (2021) expanded the therapeutic context for MSCs by demonstrating their role in neural regeneration. Their systematic review analysed 45 studies, primarily in rodent models, which explored the impact of MSCs on nerve repair processes. Across these studies, MSCs were frequently associated with enhanced axonal regrowth, remyelination, Schwann cell activation, and partial restoration of motor function, largely through paracrine signalling. Despite limitations, MSCs may target neural components of musculoskeletal injuries, such as shoulder pathologies, where dysfunction accelerates atrophy and decline. Nonetheless, rigorous clinical trials and standardised methodologies are essential before MSCs can be reliably integrated into human nerve regeneration protocols.

However, despite the encouraging outcomes, the review has several limitations decreasing its clinical relevance, particularly for translating results to sports-related nerve injuries. First, the review was limited to animal studies, with no human clinical trials included, and most models involved sciatic nerve transection or crush injuries, which may not accurately mimic chronic or traction-based nerve injuries seen in athletes. Second, variation in MSC sources, delivery routes, and outcome assessments made cross-study comparison difficult. Few studies assessed functional recovery (e.g., gait, grip strength); most relied only on histological or electrophysiological markers, limiting clinical translation. The absence of long-term follow-up in most studies and the lack of standardised MSC characterisation protocols raise concerns about reproducibility and scalability.

Despite these limitations, the preclinical evidence, derived primarily from rodent models, demonstrates that MSCs can enhance nerve repair mechanisms through neurotrophic and neuroprotective effects. This is particularly significant in sports-related shoulder pathologies, where nerve dysfunction amplifies motor deficits.

4.3.2. Emerging Muscle Progenitor Cell Contributions

Dar et al. (2024) investigated the role of muscle-residing progenitor cells, specifically identifying a novel PDGFRβ^{+} satellite cell subset, noting their heterogeneous nature and capacity for regenerative response. They compared satellite cells across muscles, concluding that gastrocnemius satellite cells had greater myogenic and adipogenic potential than those from the rotator cuff. Specifically, PDGFRβ^{+} satellite cells were shown to contribute to regeneration following chronic rotator cuff injury. Analysis revealed that these cells possess significant myogenic potential, actively participating in the differentiation of new myofibers after injury. To further explore this, the researchers conducted an animal study in which Cre activity was induced via tamoxifen administration, followed by unilateral transection of the supraspinatus and infraspinatus tendons. This methodological approach allowed for targeted investigation of the regenerative behaviour of PDGFRβ^{+} satellite cells within the injured musculature.

The model displayed irreversible degeneration of the suprascapular nerve, simulating chronic rotator cuff injury. Tissue analysis at 5 days, 2 weeks, and 6 weeks confirmed significant contributions of PDGFRβ^{+} progenitors to muscle regeneration. In addition to the regenerative capacity of these myogenic progenitors, the study also mentions an observable progression of muscular degeneration from the lateral to medial region (Dar et al., 2024). These findings highlight the broader potential of progenitor-based therapies in musculoskeletal repair, complementing tendon-focused strategies where MSC tenogenesis remains a central research priority.

4.3.3. Strategies to Enhance MSC Tenogenesis

In parallel, tendon-specific MSC therapies have continued to evolve. Citeroni et al. (2020), for example, emphasise the importance of directing MSCs towards tenogenic differentiation using well-defined in vitro protocols. Their review details strategies to optimise tendon regeneration using biochemical stimulation, mechanical loading, scaffold design, and co-culture systems. When primed, MSCs express key tenogenic markers (e.g., scleraxis, tenomodulin, collagen type I), enabling them to mimic tenocyte behaviour and enhance graft integration.

Building on these foundational approaches, Citro et al., (2025), developed electrospun polycaprolactone (PCL) fibres embedded with mesoporous silica nanoparticles loaded with

GFs such as GDF-7. This dual-cue scaffold offered both topographical stimuli, promoting MSC and tendon stem cell viability, alignment, and metabolic activity, especially under low-oxygen conditions that mirror the tendon microenvironment. The MSC system also preserves protein integrity and enables sustained release, positioning as a functional autograft alternative for tendon tissue engineering (Citro et al., 2025).

Similarly, Kent et al., (2024) reviewed fibre-reinforced hydrogel composites, which combine the mechanical strength of polymeric fibres with the biological versatility of hydrogels. These composites replicate the alignment and stiffness of native tendon, support mesenchymal progenitor cell recruitment, and promote tenogenic differentiation and matrix deposition. Their integration allows scaffolds to overcome limitations of earlier materials by supporting both mechanical performance and biological fidelity.

4.3.4. Clinical Challenges and Future Directions

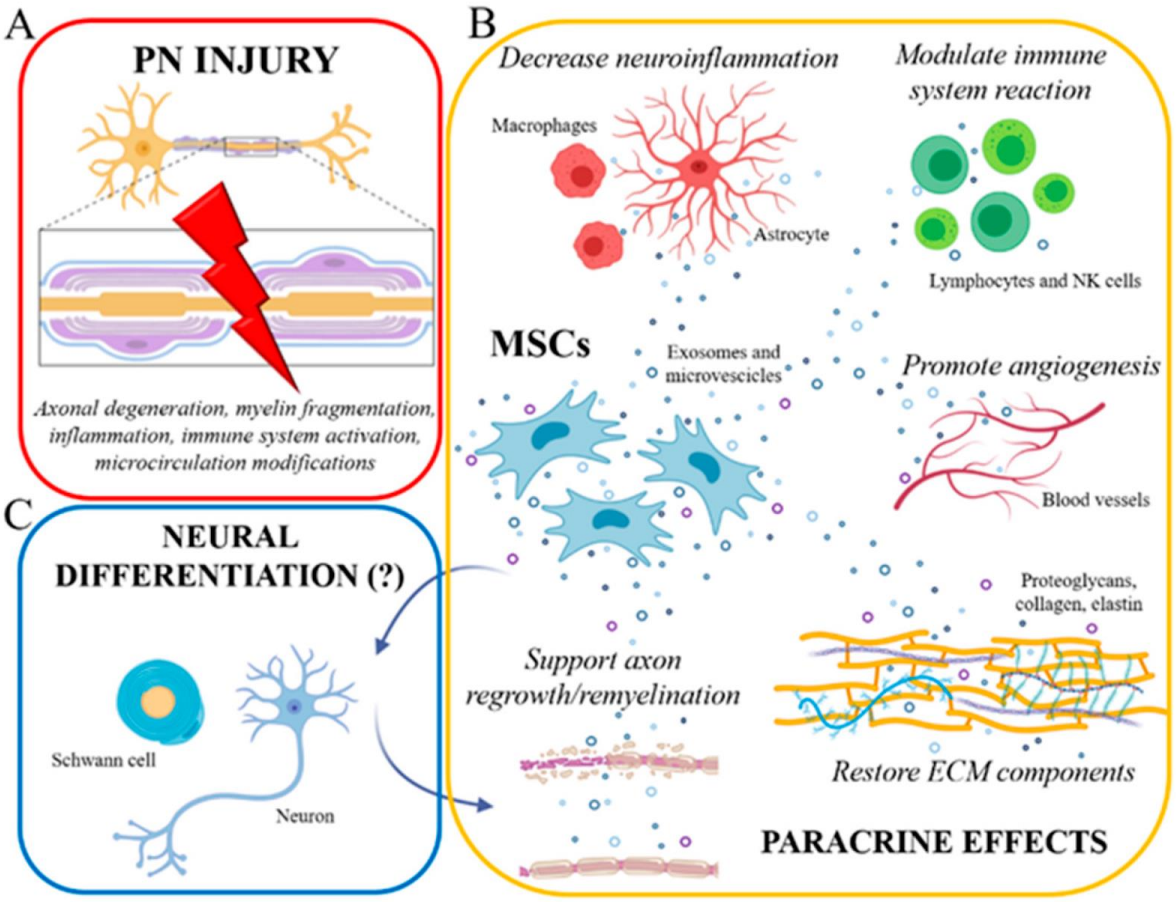
Citeroni et al. (2020) highlight the need to replicate the complex in vivo environment by incorporating hypoxia, mechanical stress, and scaffold-based delivery in MSC conditioning protocols. These methods more closely emulate native tendon biology and may improve therapeutic outcomes by encouraging ECM deposition and functional integration, outcomes that are particularly critical in athletic populations, where high mechanical demands and performance expectations necessitate durable, load-bearing tissue repair.

4.3.5. Clinical Trials and MSC–Scaffold Strategies in Rotator Cuff Repair

Clinical adoption will depend on large-scale, multicentre trials with standardised protocols for MSC expansion, delivery, and outcome evaluation. For example, ClinicalTrials.gov ID: NCT06817616 is investigating “Arthroscopic Rotator Cuff Repair with Umbilical Cord-derived Mesenchymal Stem Cells for Large to Massive RCTs.” This trial aims to explore the potential of MSCs in treating rotator cuff injuries in combination with arthroscopic repair. Since shoulder injuries often involve damage to both tendinous and neural tissues, the dual application of MSCs for tendon and nerve regeneration represents a novel and integrative approach in sports medicine and orthopaedics (see Figure 4). Although MSCs show promise for tendon healing and neural recovery, optimal host integration remains a hurdle. This challenge has sparked interest in scaffold-based systems, which provide mechanical support and a regenerative environment, complementing MSC capabilities.

Figure 4

Mechanisms of MSC-mediated peripheral nerve regeneration



Notes: (A) Peripheral nerve injury initiates a series of degenerative and inflammatory processes, including axonal breakdown, myelin fragmentation, immune system activation, and altered microcirculation. (B) MSCs exert therapeutic effects primarily through paracrine signalling, including exosome and microvesicle release. These mediators help reduce neuroinflammation, regulate immune responses, stimulate angiogenesis, restore ECM components, and support axonal regrowth and remyelination. (C) Experimental protocols have explored the potential for MSCs to differentiate into neural cell types, such as Schwann cells or neurons, to further aid regeneration. However, whether such differentiation occurs in vivo remains uncertain. Source: Adapted from Lavorato et al. (2021), created with BioRender software. .

4.4. Tissue Engineering and Scaffold-Based Regenerative Strategies

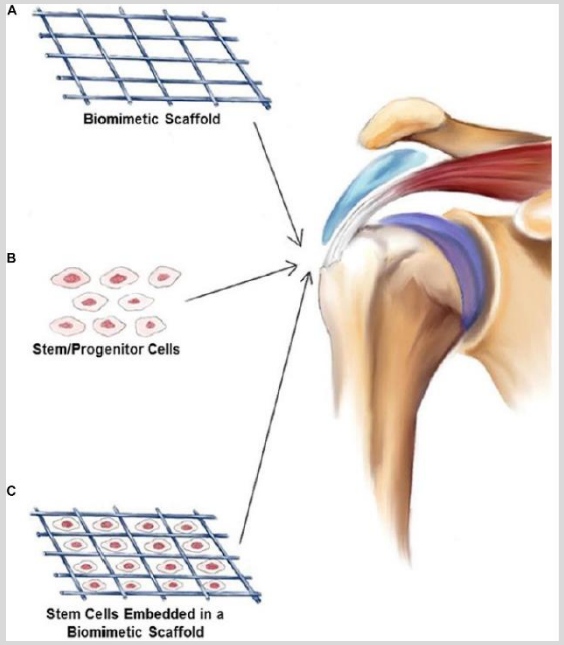
4.4.1. Introduction to Scaffold-Based Therapies

TES have emerged as promising solutions in rotator cuff repair, offering both mechanical reinforcement and biologically conducive environments for regeneration. Designed to replicate the gradient structure of the TBI, these biomaterials promote cellular adhesion, migration, and ECM deposition. Beyond providing mechanical support, scaffolds

can be functionalised to deliver MSCs, GFs, or bioactive molecules in a controlled manner directly at the injury site (Kurian et al., 2022).

Figure 5

Stem cell-scaffold strategies for tendon regeneration



***Note**:* Schematic of stem/progenitor cells embedded within scaffold materials to promote tendon regeneration (Bianco et al., 2019, as cited in Zhang et al., 2021).

4.4.2. Preclinical Successes: Collagen Composite Scaffolds

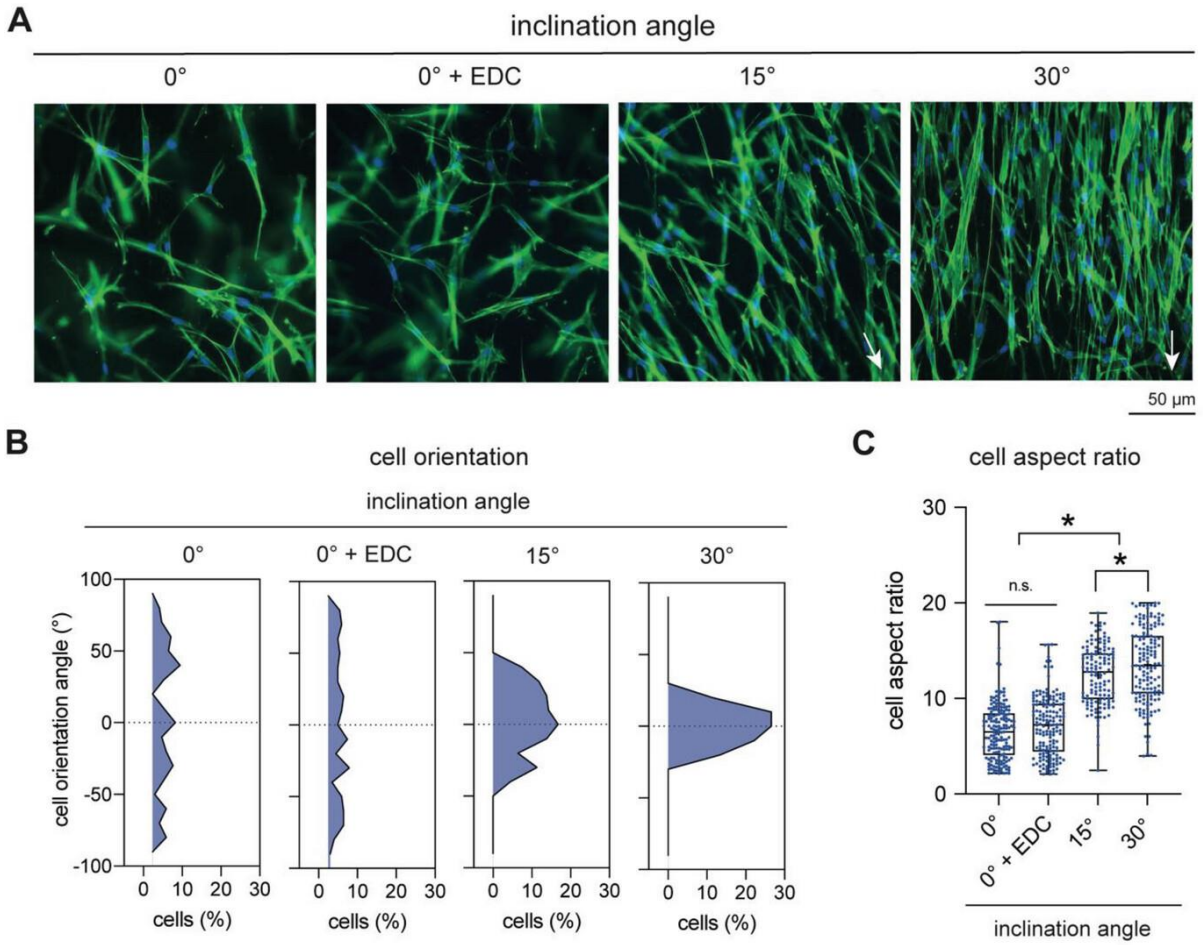
Among the materials explored, silk-collagen composite scaffolds show considerable promise. In a preclinical rabbit model, a preclinical study by (Han et al., 2023) developed a nano-calcium silicate-mineralised fish scale (CS-FS) scaffold with a Bouligand microstructure to enhance healing at the TBI. The study included a rat and rabbit RCT model, assessing outcomes up to 12 weeks post-surgery. The CS-FS group exhibited superior enthesis regeneration, with denser tissue integration, increased type I collagen expression, and improved collagen fibre alignment, as visualised by SEM and histological staining (see Figure 6).

Furthermore, gene expression analysis revealed that CS-FS scaffolds significantly upregulated osteogenic (Runx2, Opn, Ocn, Col1), chondrogenic (Sox9, Aggrecan, N-cadherin), and tenogenic (Tnc, Bgn, Col1) markers, suggesting activation of the BMP-

2/Smad/Runx2 signaling pathway and supporting enhanced tendon-bone interface regeneration (Han et al., 2023). Although the study did not assess the functional recovery or loading capacity under sport-like conditions, the enhanced fibre alignment and interface healing suggest translational potential for tendon repair.

Figure 6

Impact of collagen matrix alignment on fibroblast orientation



Notes: (A) Fluorescence microscopy images showing fibroblast alignment on reconstituted 3D collagen matrices with inclination angles of 0°, 0° + EDC crosslinking, 15°, and 30°. Increased inclination promotes visibly improved cell orientation and alignment (white arrows indicate direction). (B) Distribution plots of cell orientation angles indicate a shift toward unidirectional alignment as matrix inclination increases. (C) Quantitative analysis of cell aspect ratio reveals significantly greater elongation in the 15° and 30° groups compared to control ($p < 0.05$). These results demonstrate that aligned collagen substrates can direct fibroblast orientation and elongation in vitro, highlighting a key mechanism by which scaffold alignment could enhance organised tissue regeneration relevant to tendon repair (Sapudom et al., 2023).

In a foundational preclinical study, (P. Chen et al., 2021) evaluated the regenerative capacity of bioactive collagen scaffolds seeded with human tendon-derived cells in a human rotator cuff injury model (n=18). The composite scaffold provided a biomimetic ECM that enhanced cell adhesion, proliferation, and tenogenic differentiation. Histological analysis revealed improved collagen fibre alignment, reduced inflammatory response, and more organised enthesis formation compared to unseeded scaffolds and surgical repair alone. These findings demonstrate the synergistic effect of scaffold microstructure and cell-based therapy in promoting biologically integrated healing, supporting the rationale for integrating progenitor cells into bioengineered scaffolds for tendon repair.

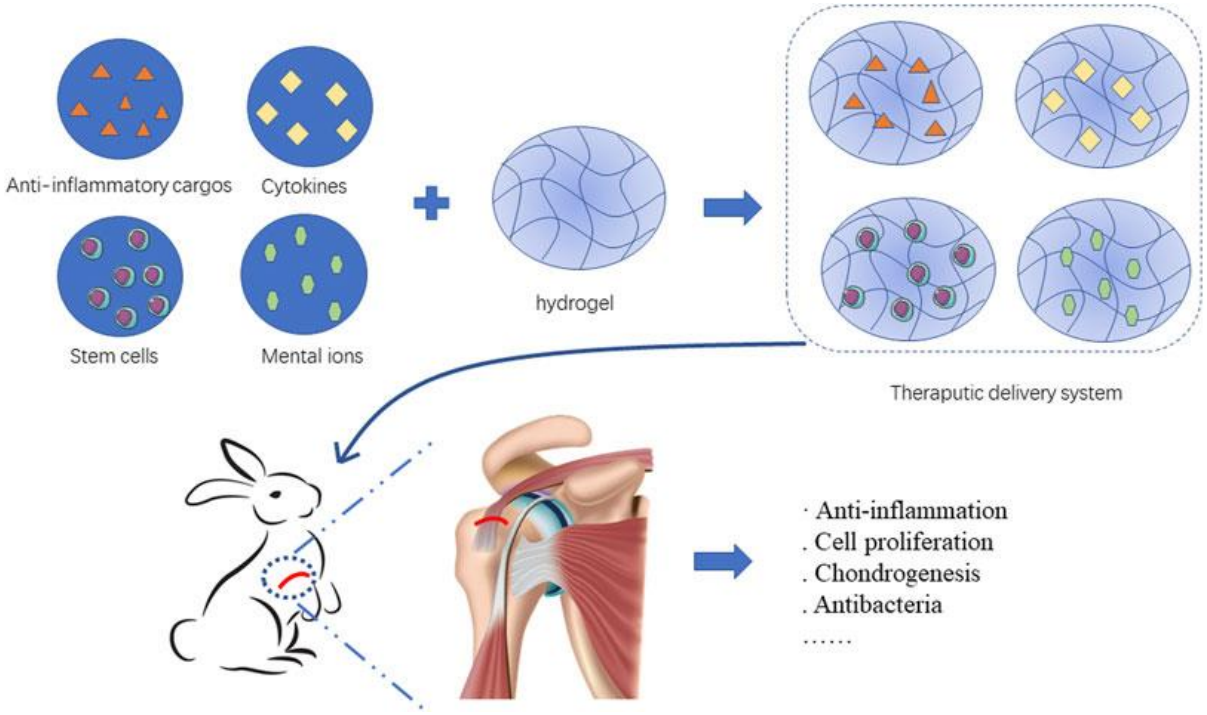
4.4.3. Hydrogels as Delivery Platforms and their Preclinical Efficacy

Hydrogels are three-dimensional (3D) crosslinked polymer networks composed of hydrophilic polymer chains, enabling them to absorb significant quantities of water and biological fluids (Khan et al., 2024; Pablos et al., 2024; Xu et al., 2022). These biomaterials are highly valued for their ability to mimic the ECM (ECM), offering an ECM-like growth environment for cells (Chen et al., 2024; Xu et al., 2022). They possess excellent biocompatibility, biodegradability, and elasticity, closely resembling living tissues and facilitating tissue regeneration and cell adhesion (Pablos et al., 2024; Xu et al., 2022). Beyond their structural properties, hydrogels can also serve as carriers for cells or other therapeutic substances as shown in Figure 7, effectively delivering nutrients and biofactors with minimal immune reactivity, thus supporting endogenous regeneration and biological repair (Chen et al., 2024; Xu et al., 2022).

In regenerative medicine, hydrogels present a promising approach for addressing complex injuries, particularly in the context of RCTs (Chen et al., 2024; Xu et al., 2022). Hydrogel scaffolds act as effective delivery systems that can improve RCT healing and potentially treat irreparable injuries (Xu et al., 2022). For successful repair, these hydrogels must meet several requirements: they should replicate the multi-regional structure, matrix composition, microstructure, and mechanical characteristics of the native tissue interface; support the adhesion, proliferation, and differentiation of specific stem or progenitor cells; and degrade at a rate synchronised with tissue regeneration (Chen et al., 2024; Xu et al., 2022).

Figure 7

Hydrogels as multifunctional carriers for rotator cuff healing



Notes: Schematic of hydrogels functioning as versatile carriers for therapeutic cargo: anti-inflammatory agents, cytokines, stem cells, and metal ions, directed towards the promotion and facilitation of rotator cuff healing (Xu et al., 2022).

To meet these requirements, their mechanical properties are crucial for stimulating cell differentiation and integrating with surrounding tissues, allowing for the sustainable release of bioactive components that promote healing and minimise inflammation in the challenging TBI environment (Chen et al., 2024). As emphasised by Xu et al. (2022), 20-70% continue to experience rotator cuff dysfunction postoperatively, mainly due to poor TBI healing, and scar tissue formation. They proposed that hydrogels, combining natural and synthetic materials like GelMA and PEDGA, could reduce these dysfunction rates by creating a conductive microenvironment for stem cells and GFs, thus enhancing tissue regeneration.

Kataoka et al. (2021) conducted a controlled study in rats (n=10 per group, 4 total groups), comparing gelatin-hydrogel sheets impregnated with PBS (control), PRP, Basic fibroblast growth factor (bFGF) and combination of PRP and bFGF. In their model, the tendon maturing score for the combined was group was significantly higher (6.3) than the control (4.1, $p<0.05$). Biomechanical testing at 6 weeks post-surgery demonstrated that the ultimate failure

load in the combined group was 19.3 ± 3.2 N, whereas the control group's ultimate failure load was 12.5 ± 2.6 N ($p<0.01$). Although effective, the model and lack of return-to-function metrics limit applicability to chronic overuse injuries in athletes.

By further supporting these results, Oda et al., (2023) tested a thermoresponsive tendon hydrogel loaded with adipose-derived stem cells (ADSCs) and PRP in a chronic rat model (n=33). After 8 weeks, the failure load in the concentrated PRP group was 14.9 ± 2.7 N, which was far greater than the score achieved by the control group: 10.3 ± 1.9 N ($p<0.01$). Additionally, there was a noted improvement in stiffness (17.2 ± 3.1 Nmm^{-1} vs. 12.0 ± 2.5 Nmm^{-1}). Yet, no dose-dependent effects were confirmed, and functional limb use was not assessed. While promising, translating these biomechanical gains into sport-relevant recovery remains uncertain.

Hydrogels also show promise in muscle quality preservation, a key factor in long-term functional recovery, especially for athletes. Pfaff et al. (2025) demonstrated that viscoelastic hyaluronic acid hydrogel in a murine model of delayed repair reduced muscle atrophy by ~32% and fatty infiltration by ~30% compared to controls. These effects highlight the ability of hydrogels to be able to improve the TBI but also to enhance surrounding muscle health, which is often overlooked regarding rotator cuff healing.

4.4.4 Future Directions: Multi-Tissue and Zonal-Specific Scaffolds

Building on this broader regenerative perspective, Li et al. (2025) introduced an injectable piezoelectric hydrogel that modulates the electrophysiological environment at the repair site, promoting M2 macrophage polarisation and zonal-specific differentiation of bone mesenchymal stem cells (BMSCs). Their hydrogel exhibited robust mechanical properties, with a shear strength of 29.136 kPa, fracture strength of 110.74 kPa, and tensile strength of 388.57 kPa, reflecting improvements in adhesion and load-bearing performance. Also, in vitro studies revealed significantly higher osteogenic (OPN, RUNX2) and tenogenic (TNMD, Scx) marker expression in the Piezo-3 μA and Piezo-5 μA groups at 7 days ($p<0.01$) compared to controls.

4.4.5. Challenges in Clinical Translation of Scaffold-Based Therapies.

Another challenge is the lack of standardisation across scaffold design and surgical application; for example, studies differ widely in scaffold composition, porosity, degradation

rates, and surface topography. Furthermore, discrepancies in fixation techniques, surgical placement, and post-operative rehabilitation protocols introduce additional variability. This heterogeneity makes it difficult to perform meta-analyses or establish consistent clinical guidelines.

An emerging solution to the limitations of single-phase scaffolds is the development of stratified, multi-tissue scaffolds that mimic the native gradient of the TBI. These constructs incorporate phase-specific mechanical and biochemical cues to promote zone-specific cellular responses, facilitating the regeneration of tendon, fibrocartilage, and bone in a spatially controlled manner. Such scaffolds aim to replicate the hierarchical structure of the enthesis, restoring mechanical continuity and minimising stress concentrations that contribute to graft failure. Advanced fabrication methods, such as electrospinning and 3D bioprinting, are increasingly employed to engineer these scaffolds with microscale precision, enabling the integration of osteoinductive and tenogenic factors within discrete compartments. By tailoring scaffold architecture to recapitulate in vivo loading and structural heterogeneity, these innovations represent a critical advancement toward functional and durable tendon-bone healing in rotator cuff repair (Zhang et al., 2022).

Figure 8

Key growth factors in tendon repair and their biological roles

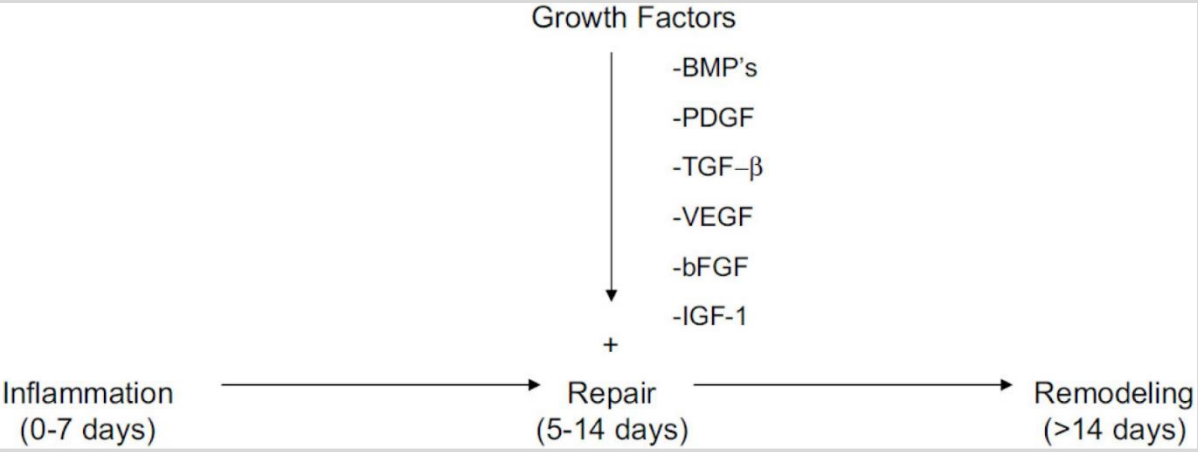
Growth factor	The phase in which the growth factor most active	Roles
IGF-1	Inflammation	Promotes the proliferation and migration of cells, stimulates matrix production
	Proliferation	
TGF-β	Inflammation	Regulates cell migration, proteinase expression, fibronectin binding interactions, termination of cell proliferation, and stimulation of collagen production
VEGF	Proliferation	Promotes angiogenesis
	Remodeling	
PDGF	Proliferation	Regulates protein and DNA synthesis at the injury site, regulates the expression of other growth factors
	Remodeling	

Note: Overview of biological GFs involved in tendon repair and regeneration, highlighting their roles in angiogenesis, cell migration, and collagen production (Molloy et al., 2003, as cited in (Zhang et al., 2021).

Despite these limitations, scaffold-based tissue engineering remains a compelling avenue for enhancing rotator cuff repair, particularly when combined with biologics like MSCs and PRP. Recent approaches explore incorporating growth factor gradients or controlled drug release into scaffold matrices to mimic natural healing cascades more closely (see Figure 8 and Figure 9). To unlock the full potential of these technologies, future research must focus on improving scaffold biomechanics, ensuring long-term biocompatibility, and validating efficacy through well-designed, randomised clinical trials with robust imaging and functional outcomes. Integrating scaffold use into standardised regenerative protocols may offer a meaningful step forward in managing complex or degenerative rotator cuff injuries.

Figure 9

Phases of rotator cuff healing: Inflammation, repair, and remodeling



Notes: Phases of healing following RCI, including initial inflammation, tissue repair, and final remodelling (Gulotta & Rodeo, 2009, as cited in Zhang et al., 2021).

5. Conclusion

Recent research underscores the transformative potential of regenerative medicine for shoulder injuries, particularly through stem cell augmentation and advanced scaffold-based strategies. Clinical and preclinical studies have demonstrated that MSCs can enhance tendon healing, reduce fatty infiltration, and modulate inflammation. TES has evolved to mimic the hierarchical structure of the TBI, providing both mechanical support and biologically relevant cues that promote tenogenic and osteogenic differentiation. Hydrogels incorporating MSCs or GFs have shown efficacy in preserving muscle quality and promoting enthesis regeneration.

However, heterogeneity in study design, inconsistent MSC and PRP protocols, and the absence of long-term, standardised clinical trials remain major barriers to clinical translation. Moving forward, rigorous multicentre trials and homogenous methodologies will be essential to establish reliable regenerative treatments capable of restoring tendon structure and function, ultimately improving outcomes for athletes and patients with complex injuries.

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