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MEDICINE

# A Critical Review of Regenerative Therapies for Shoulder Rotator Cuff Injuries

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## Abstract

Rotator cuff tears can cause pain and weakness in the shoulder and affects a wide range of individuals. Conventional repair consists of operative surgical techniques or conservative treatments including physiotherapy; however, there is still a big issue in the increased risk of re-tearing of the tendons. Regenerative therapies are looking for new and novel ways of improving the healing of tendon injuries. Platelet-rich plasma (PRP) uses the patient's own blood in a concentrated form, to supply the repair site with various growth factors that promote the healing response; however, research shows conflicting evidence about the efficacy and effectiveness of PRP. Stem cell research is slowly increasing use of human patients in research trials and is showing significant results in improving and reducing the re-tear rate. Tissue engineering encapsulates a range of techniques such as scaffolds and patches to augment repair of the rotator cuff tendon, and research has shown that such techniques can provide protection and assistance to the repairing tendon to improve results. This review aims to critically compare and evaluate recent research and provide possible future directions.

**Keywords** Platelet-rich plasma · Stem cells · Tissue engineering · Mesenchymal stem cells · Scaffolds · Augmentation · Re-tear

## Introduction

The rotator cuff (Fig. 1) is a group of four muscles (the supraspinatus, infraspinatus, teres minor, and subscapularis) in the glenohumeral joint (GHJ). Rotator cuff tears (Fig. 1) can cause pain and weakness in the shoulder. It is an injury that plagues the general public (4% of under 40's; 53% of over 60's) and athletes alike [1]. Repair is often either non-operative, utilising physiotherapy to maintain range of movement, rotator cuff, and deltoid strength, as well as scapula-stabilising or operative, which employs surgical methods to repair and reattach the tendon; however, it can lead to re-tearing, persistent pain, and stiffness [2].

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Classification of a rotator cuff injury is often based on the size of the tear (Table 1) [2]. Healing rates are poor for surgical repairs of large and massive tears. Novel techniques are looking at enhancing the tendon tissue regeneration. Such techniques include the use of platelet-rich plasma (PRP), a substance that when injected releases various growth factors that play a role in tissue repair; the use of stem cells, usually mesenchymal stem cells (MSCs), which have the ability to self-renew and differentiate to various tissues [3]; and the use of tissue-engineered approaches which use various scaffolds and patches to augment repair [4, 5]. The aim of this review is to critically analyse the new regenerative therapies that have been used recently to facilitate healing following rotator cuff injuries.

## Novel Strategies Used in Rotator Cuff Regeneration

Regenerative therapies utilised in rotator cuff regeneration all differ in their application. PRP therapy is a form of prolotherapy and requires patients to undergo injections, often post-surgery; stem cell therapy requires the patient to undergo surgery, with stem cells being applied following surgery; and tissue engineering is a relatively new approach and covers a

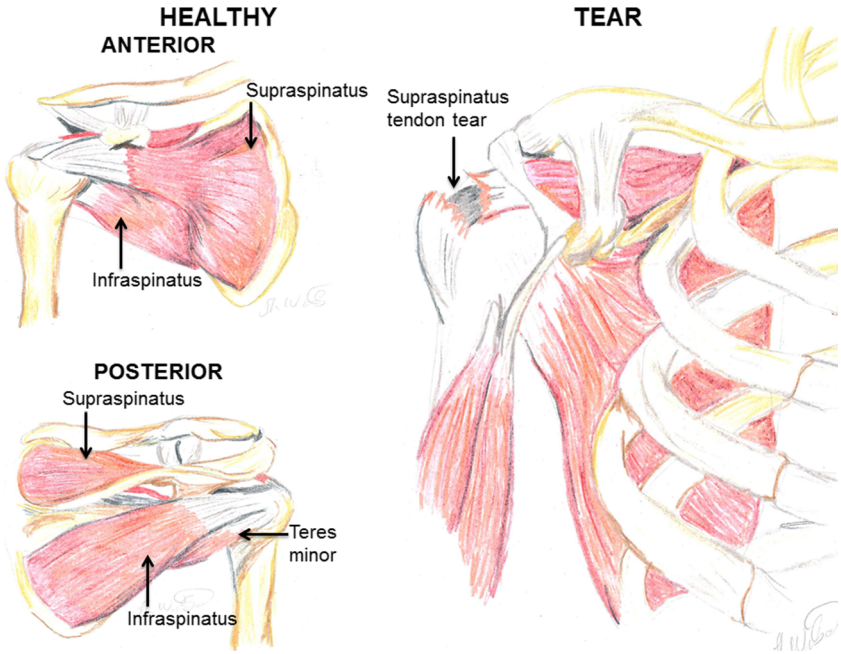


**Fig. 1** Healthy anterior and posterior views of the rotator cuff muscles (left). Example of a rotator cuff tear (supraspinatus) (right)

range of techniques, such as utilising scaffolds and patches to augment surgery. PRP has predominantly been studied on humans, although results are still not clear as there are numerous contradictory findings. Stem cell research has been shown to reduce the rate of re-tears, although there have currently been limited studies on humans to date. Tissue engineering is providing novel techniques with very promising results, although not one 'gold-standard' has been determined for rotator cuff repair. Research has used a variety of scores and scales (Table 2) to assess quality of repair.

PRP has been utilised to augment surgical repair of medium and large tears [6], resulting in a significantly improved repair, as there was a significant improvement (decrease) in the re-tear rate. Pandey et al. [7] investigated the use of PRP to aid in the healing of large and massive rotator cuff repairs [7]. Similarly, a decreased re-tear rate was found 24 months post-surgery for large tears, when compared to a control group of 50 patients. Results also demonstrated that PRP can reduce pain and increase functionality, strength, and vascularisation post-surgery.

Hernigou et al. [8] and more recently Kim et al. [9] have provided the most comprehensive research when focusing on stem cell therapy [8, 9], both indicating that stem cells can improve rotator cuff surgery, especially improving (decreasing) re-tear rates post-surgery, which is one of the main concerns following surgical tendon repair. Any disruption (re-tear) in the initial healing stage can interfere with rehabilitation strategies, resulting in a prolonged time frame before patients can resume full activities (work or sport).

Tissue engineering approaches have utilised various scaffolds and patches to augment healing, such as 'GraftJacket' [10]. Results show that the use of this acellular human dermal matrix augmentation can improve the quality of repair, as more intact rotator cuffs were found (85% compared to 40%), as well as improving various scores on pain and function, compared to surgical repair with no additional augmentation.

**Table 1** Classification of rotator cuff tears by size

| Classification | Tear size (cm) |
|---|---|
| Small | < 1 |
| Medium | 1–3 |
| Large | 3–5 |
| Massive | > 5 |

## Critique of Techniques Used in Rotator Cuff Regeneration

### Platelet-Rich Plasma

Of all the regenerative techniques that will be critiqued in this review, the use of platelets has been investigated in humans more than studies in stem cell research and tissue-engineered approaches. This could suggest that the use of platelets is already becoming an accepted practice since it carries less ethical issues.

Literature demonstrates (Table 3) that there are mixed, sometimes, conflicting results, following the use of PRP. Studies that adopted a human model reported a significant improvement in scores (Table 2) such as the VAS, Constant-Murley score, UCLA, and shoulder external rotation [6, 7, 13, 22]. When evaluating the actual injuries that were reported in

**Table 2** Scores and scales used to evaluate intervention effectiveness

| Score/Scale | Measure | Key points |
|---|---|---|
| Visual analogue scale (VAS) | Pain | Subjective, a 0–10 scale, patients mark the scale. |
| Constant-Murley score (constant) | Functionality | Subjective and objective. Four subscales: pain; activities of daily living, strength, and range of movement |
| University of California, Los Angeles (UCLA) | Strength and function | Subjective and objective. Measures, forward elevation, strength, pain, satisfaction, and function |
| American Shoulder and Elbow Surgeons (ASES) | Pain and function | Subjective and objective. Includes physician-rated section. Measures pain, function, and instability. |

these studies, participants were only included if they had suffered rotator cuff tears, whereas studies that reported no significant differences often only looked at tendinopathy [11, 14]. This may suggest that PRP could be more effective in the treatment of a full tear. Perhaps during tendinopathy, there has already been some degree of healing, meaning that the additional growth factors and stimulation PRP promotes are not effective and can only help in the initial stages of 'tendon-bone' formation.

This is verified by animal studies (rabbits and rats) that created and repaired acute tears, where all results showed significant improvement with the use of PRP. Improvements included an increase in vascularisation and cellularity within 4 weeks [20] post-treatment and fibronectin production [19], suggesting that PRP does benefit healing, however, only in the initial stages. These studies used animal models (rabbits and rats); thus, the results cannot be completely generalised to humans.

Interestingly, there have been human studies that investigated the use of platelet-rich fibrin (PRF) instead of the more conventional PRP. Platelet-rich fibrin (or platelet-rich fibrin matrix (PRFM)) is a variation of PRP and involves activation of the fibrin-clotting cascade and a second centrifuge stage [15]. As PRF is already formed into a matrix, it traps some non-activated platelets, essentially delaying the release of platelets and providing a longer time frame for platelet delivery. Yet again, results were varied, with Antuña et al. [23] showing improvements whereas Rodeo et al. [15] and Weber et al. [16] reported no significant differences to healing. Although Antuña and colleagues (Antuña et al. [23]) did report significant differences in shoulder function (constant score increased) and pain scores (VAS decreased), their results might not carry much statistical power as the population size of their study was small ($n = 28$). These findings could suggest that the use of PRF does not improve the healing of the tendon-bone interface, perhaps due to gaps that are left behind once the matrix has dissolved [15].

The majority of studies (animal models that found a significant improvement) reported an increase in the maximum load to failure. This suggests that PRP can create a stronger 'bond' than that created naturally. This could be linked to the increased vascularity reported earlier, as the repair site would experience an increase in growth factors and inflammatory cells to aid in the reparative and remodelling stages.

## Stem Cells

When evaluating the use of stem cells (Table 4) in the regenerative therapies of rotator cuff injuries, there are few studies that have investigated the application of stem cells in humans, although they have shown promising results. As early as 2012, Gomes et al. found that an injection of autologous bone marrow (BM) mononuclear cells following surgery increased patient's functional status [34]. However, since there was no control group, results could only be compared to histological data; since the study was not blinded, there was the possibility of bias in the results; coupled with small population size, the statistical relevance of these results is questionable.

Of the three human studies included in this review, only one did not use BM-derived MSCs. Kim et al. [9] utilised adipose tissue (AT)–derived MSCs in combination with fibrin glue, delivering mechanical aid whilst delivering MSCs. BM is considered to be a favourable source of MSCs [35] and is still being found to give the most beneficial effects in tendon healing [36]. However, sourcing MSCs from AT is less painful, and there is a greater concentration of stem cells, which would be desirable, as Hernigou et al. [8] alluded to. The number of MSCs is important, since fewer MSCs included in the applied solution may result in reduced tendon integrity, which in turn could come full circle and result in a re-tear. The study by Kim et al. [9] shows an alternative to BM as a source for stem cells in the regenerative repair of the human rotator cuff.

When comparing the animal studies that have used stem cells to aid the healing, the majority have shown fairly positive results, with only two studies finding no significant differences. Of these two, one was an early study [33, 37] which included one of the shortest follow-up times of a maximum of 4 weeks, leaving the possibility that they might have

**Table 3** Platelet-rich literature comparison of studies

| Reference | Model | Injury type | Intervention | Control | Significant findings |
|---|---|---|---|---|---|
| Pandey et al. 2016 [7] | Human model | Medium and large degenerative posterosuperior tears | Surgery and PRP ($n = 52$) | Surgery alone ($n = 50$) | VAS ↓ @ 1, 3, and 6 months<br>Constant-Murley score ↑ at 12 and 24 months.<br>UCLA ↑ at 6 and 12 months.<br>Re-tear rate ↓ at 24 months (only for large tears).<br>Ultrasound—↑ vascularisation at 3 months. |
| Carr et al. 2015 [11] | Human model | Rotator cuff tendinopathy | Treatment group ($n = 25$) received surgery + PRP | Surgery alone ($n = 23$) | – |
| Jo et al. 2015 [6] | Human model | Medium to large tears | PRP-augmented repair ($n = 37$) | Conventional repair ($n = 37$) | Re-tear rate ↓ |
| Malavolta et al. 2014 [12] | Human model | Complete supraspinatus tears | Surgery and PRP with autologous thrombin ($n = 27$) | Surgery alone ($n = 27$) | – |
| Antuña et al. 2013 [13] | Human model | Massive rotator cuff tear | Treatment group ($n = 14$) received 6 ml PRF (Vivostat®) | Surgery alone ($n = 14$) | |
| Kesikburum et al. 2013 [14] | Human model | Chronic rotator cuff tendinopathy | PRP group ($n = 20$) | Placebo group ($n = 20$) | – |
| Rodeo et al. 2012 [15] | Human model | Rotator cuff tear | Surgery and received PRFM at tendon-bone interface ($n = 40$) | Surgery alone ($n = 39$) | – |
| Weber et al. 2012 [16] | Human model | Rotator cuff tear | Platelet-rich fibrin matrix ($n = 30$) | No treatment control group ($n = 30$) | – |
| Randell et al. 2011 [17] | Human model | Complete rotator cuff tear | PRP and autologous thrombin component ($n = 26$) | No treatments ($n = 27$) | Pain ↓ at 3, 7, 14, and 30 weeks<br>UCLA and external rotation strength ↑ at 3 months.<br>SER ↑ 2 years post-op. |
| Dolkart et al. 2014 [18] | Rat Model | Supraspinatus tear | Experimental group ($n = 22$) repair and PRP; | Repair only ($n = 22$) | Maximum load and stiffness ↑<br>Bonar score ↑<br>Collagen birefringence ↑ |
| Lamplot et al. 2014 [19] | Rat model | Supraspinatus tear | PRP group ($n = 8$)<br>AdBMP13 group ($n = 8$);<br>PRP + AdBMP13 group ($n = 8$) | Adenovirus-containing green fluorescent protein (AdGFP, negative control) ($n = 8$) | BMP13 upregulated collagen type III compared to control and PRP; BMP13 and PRP upregulated fibronectin.<br>Stress to failure ↑ |
| Chung et al. 2013 [20] | Rabbit model | Supraspinatus tear | Repair (R) ($n = 20$)<br>Repair + patch (RPa) ($n = 20$)<br>Repair + PRP (RPr) ($n = 20$)<br>repair+ patch + PRP (RPaPr) ($n = 20$) | Left shoulder for control | 4 weeks—vascularity and cellularity ↑<br>8 weeks—collagen fibre continuity ↑<br>Load to failure significantly different between R and RPr, and R and RPaPr, and RPa and RPaPr |
| Wu et al. 2014 [21] | Rabbit model | Rotator cuff tear | PRP group ($n = 10$)<br>PRP group ($n = 10$) | Surgery alone ($n = 10$) | Maximum load ↑ with PRP + BG group at 6 weeks<br>Better tendon-bone healing in PRP + BG at both time points and more organisation seen at 12 weeks |

Ordered by 'Model', with studies using a human model coming first. *PRP*, platelet-rich plasma; *PRF*, platelet-rich fibrin; *PRFM*, platelet-rich fibrin matrix; *BG*, bioactive glass; *AdBMP*, adenovirus-mediated BMP13; *VAS*, visual analogue scale (pain); *UCLA*, University of California, Los Angeles; *SER*, shoulder external rotation

**Table 4** Comparison of stem cell literature

| Reference | Model | Injury type | Intervention | Control | Significant findings |
|---|---|---|---|---|---|
| Kim et al. 2017 [9] | Human model | Full thickness rotator cuff tear | Surgery and adipose-derived MSC in a fibrin glue injection ($n = 35$) | Surgery alone ($n = 35$) | Re-tear rate ↓ |
| Hernigou et al. 2014 [8] | Human model | Rotator cuff tear | Iliac crest–derived bone marrow MSC ($n = 45$) | Surgery alone ($n = 45$) | 100% of repairs with MSC had healed at 6 months vs 67% of control.<br>87% of MSC repaired were still intact vs 44% of control at 10 years |
| Ellera Gomes et al. [24] | Human model | Rotator cuff tear | Surgery and injection of autologous BMMC (iliac crest) ($n = 14$) | – | Tendon integrity in all cases<br>UCLA ↑ after 12 months |
| Sevivas et al. [25] | Rat model | Bilateral 2—tendon massive rotator cuff tear | Surgery and human MSC's (secretome) injections (4 experimental groups), single local injection group ($n = 8$), multiple local injections group ($n = 7$), single systemic injection group ($n = 8$), and multiple systemic injection group ($n = 7$). | Control/sham surgery group ($n = 7$)<br>Lesion control group ($n = 7$) | 8 weeks—single or multiple systemic injections decrease fat content.<br>16 weeks—protective effect in multiple systemic injections, single local, and multiple local compared to lesion control |
| Degen et al. [26] | Rat model | Unilateral detachment and transosseous repair of supraspinatus | Surgery and fibrin glue with BM MSC's ($n = 26$) | Surgery and fibrin glue ($n = 26$) | 2 weeks—fibrocartilage formation, coherence, failure load, and stiffness ↑; ↓ energy<br>4 weeks—no differences |
| Barco et al. [27] | Rat model | Detachment and repair of supraspinatus muscle-tendon | Surgery and adipose-derived stem cells in fibrin sealant ($n = 8$) | Surgery alone ($n = 8$)<br>Surgery and fibrin sealant ($n = 8$) | Different inflammatory response (less neutrophils and higher presence of plasma) |
| Park et al. [28] | Rabbit model | Full thickness subscapularis tendon tear | Surgery and human umbilical cord blood-derived MSC's injection ($n = 10$) | Surgery and hyaluronic acid group ($n = 10$)<br>Surgery and saline group ($n = 10$) | Tendon tear ↓<br>Walking distance, fast-walking time, and mean walking speed ↑ |
| Oh et al. [29] | Rabbit model | Bilateral subscapularis | Surgery and ADSC ($n = 8$)<br>Surgery and saline ($n = 8$)<br>ADSC ($n = 8$) | Surgery alone ($n = 8$)<br>Surgery and saline only ($n = 8$) | Surgery and ADSC ↑ compound muscle action potential area than surgery and saline<br>Surgery and ADSC—fatty infiltration ↓ (not lower than control) |
| Gulotta et al. [30a] | Rat model | Unilateral detachment and repair of supraspinatus | Surgery and MSC's transduced with adenoviral-mediated gene transfer of human BMP-13 ($n = 30$) | Surgery and untransduced MSC's ($n = 30$) | – |
| Gulotta et al. [31b] | Rat model | Unilateral detachment and repair of supraspinatus | Surgery and MSC's transduced with adenoviral-mediated scleraxis ($n = 30$) | Surgery and MSC's in a fibrin carrier ($n = 30$) | 2 weeks—ultimate stress to failure and stiffness ↑<br>4 weeks—fibrocartilage, ultimate load to failure, ultimate stress to failure, and stiffness values ↑ |
| Gulotta et al. [32] | Rat model | Unilateral detachment and repair of supraspinatus | Surgery and adenoviral MT1-MMP transduced MSC's ($n = 30$) | Surgery and adenoviral MT1-MMP transduced MSC's ($n = 30$) | 2 weeks—no difference<br>4 weeks—fibrocartilage, ultimate load to failure, stress to failure, and stiffness values ↑ |
| Gulotta et al. 2009 [33] | Rat model | Detachment and repair of the supraspinatus tendon | Surgery and adenoviral MT1-MMP transduced MSC's ($n = 30$) | Carrier alone ($n = 30$)<br>Nothing at repair site ($n = 30$) | – |

Ordered by 'Model', with studies using a human model coming first. *MSC*, mesenchymal stem cells; *BMMC*, bone marrow mononuclear cells; *ADSC*, adipose-derived stem cells; *UCLA*, University of California, Los Angeles

**Table 5** Comparison of tissue-engineering research strategies

| Reference | Model | Injury type | Intervention | Control | Outcome |
|---|---|---|---|---|---|
| Schwab et al. 2018 [38] | Human model (case study) | Subscapularis tendon tear and tendinopathy | Autologous tenocyte implementation | – | MRI—tendon completely healed<br>Dynamometry shoulder strength—return to baseline post 6 weeks |
| Lenart et al. 2015 [39] | Human model | Massive or recurrent rotator cuff tears | Synthetic poly-L-lactide patch augmentation ($n = 13$) | – | ASES ↑ |
| Cho et al. 2014 [40] | Human model | Massive rotator cuff tears | Porcine dermal patch ($n = 5$) | – | VAS, UCLA, and ASES scores ↑<br>MRI—4/5 had full intact rotator cuffs at 8 months |
| Proctor 2014 [41] | Human model | Large to massive rotator cuff tears | Poly-L-lactic lactide synthetic patch (x-repair) ($n = 18$) | – | Ultrasound—15/18 had intact rotator cuffs at 12 months. ASES ↑ |
| Barber et al. 2012 [10] | Human model | Rotator cuff tears | Acellular human dermal matrix augmentation (GraftJacket) ($n = 22$) | Control group ($n = 20$) no augmentation | ASES and Constant scores ↑ MRI—higher percentage of intact cuffs with intervention |
| Moffat et al. 2008 [42] | Human model | Rotator cuff | poly (lactide-co-glycolide) (PLGA) nanofiber-based scaffold (aligned fibre; $n = 5$) | Scaffold with unaligned fibres ($n = 5$) | Mechanical properties of aligned nanofibers higher than unaligned |
| Burkhead et al. 2007 [43] | Human model | Massive rotator cuff tears | Surgical repair augmented with GraftJacket | – | Pain, functional status, and active forward flexion ↑ |
| Omea et al. 2012 [44] | Cadaveric (human shoulder) | Rotator cuff tear | Acellular human dermal matric graft (GraftJacket) | Single row repair as control on contralateral shoulder | Maximum load ↑<br>Linear stiffness ↓ |
| Thangarajah et al. 2017 [45] | Rat model | Unilateral detachment of the supraspinatus tendon | Acellular human dermal matrix (GraftJacket) (cortical bone) ($n = 6$) | Demineralised bone matrix ($n = 6$)<br>Non-augmented repair ($n = 6$) | ↑ Organisation |
| Zheng et al. 2017 [46] | Rabbit model | Massive rotator cuff tear | Advanced 3D aligned collagen/silk scaffold (ACS) | Left shoulder/defect = ACS; right = sponge collagen/silk scaffold ($n = 20$) | 24 h—↑ alignment of tendon stem/progenitor cells<br>7 days—extracellular matrix deposited<br>12 weeks—regenerative tendon of ACS ↑ microstructures and mechanical properties |
| Huegel et al. 2016 [47] | Rat model | Bilateral supraspinatus tendon repair | Autologous tendon–derived cell-seeded polycaprolactone scaffolds ($n = 60$) | Left shoulder—acellular scaffold | 8 weeks—juvenile and aged had increased organisation and cellularity as well as mechanical improvements in treated limbs. |
| Islam et al. 2015 [48] | Rabbit model | Infraspinatus defect | Bioscaffold woven from pure collagen threads | (Compared to intact infraspinatus and regular direct repair) | Failure load and displacement at failure similar to regular repair, but half of that of the intact infraspinatus. |
| Chang et al. 2009 [49] | Rabbit model | Infraspinatus tendon detached from greater tuberosity | Right limb (intervention) periosteal flap taken from proximal end of tibia and sutured onto the tendon | Left limb (control) | Histological analysis—fibrous layer ↑<br>8 and 12 weeks— strength of limb ↑ |
| Funakoshi et al. 2007 [50] | Rabbit model | Infraspinatus tendon tear | Fibroblast-seeded scaffold ($n = 16$) | Non-fibroblast seeded scaffold ($n = 16$)<br>Defect left free ($n = 16$) | Fibroblast seeded scaffold—↑ regeneration tissue and type 1 collagen<br>4 to 12 weeks—strength and tangent modulus ↑ |

**Table 5** (continued)

| Reference | Model | Injury type | Intervention | Control | Outcome |
|---|---|---|---|---|---|
| Nicholson et al. 2007 [51] | Sheep model | Bilateral infraspinatus tears | Acellular porcine dermal (PD) patch ($n = 6$)<br>Porcine small intestine submucosa (SIS) patch ($n = 5$) | Repaired with suture alone ($n = 5$) | 3 weeks—suture and SIS significant ↑<br>9 weeks—mean failure load higher in PD than SIS shoulder undergoing PD always higher than contralateral suture or SIS repair. SIS materials absorbed.<br>24 weeks—failure loads identical, PD patch had integrated, SIS repair showed diverse tissue types. |
| Chang et al. 2009 [49] | Rabbit model | Infraspinatus tendon detached from greater tuberosity | Right limb (intervention) periosteal flap taken from proximal end of tibia and sutured onto the tendon | Left limb (control) | Histological analysis—fibrous layer ↑<br>8 and 12 weeks—strength of limb ↑ |

Ordered by 'Model', with studies using a human model coming first. *MRI*, magnetic resonance imaging; *VAS*, visual analogue scale; *UCLA*, University of California, Los Angeles; *ASES*, American Shoulder and Elbow Surgeons score

overlooked any potential prolonged benefits. Further study by Gulotta (2011a) looked at two different variations of MSCs, demonstrating that there was no difference between these variations. However, following the trend from other research (Table 4), it would be wise to assume that there would be some additional benefits in using MSCs than just surgery alone.

It is possible to see (Table 4) animal studies show varying degrees of success and analyse a range of different outcome measures, for example maximum load at failure, cartilage formation, and fat content. Kim et al. [9] suggested that follow-up should be 12 months at least, as most re-tears happen within 6 months [35]. With the animal studies having a short follow-up period and providing potentially subjective histological analysis, data may be missing the requirements for long-term recovery; however, more human trials would need to look at these factors in similar time frames to confirm that. Additionally, rehabilitation that humans undertake post-surgery could pose as an added risk for re-tears.

## Tissue Engineering

When examining the numerous tissue-engineering approaches in the regeneration of tissue, most have utilised grafts and scaffolds, with most studies presented in this review showing positive results (13 of 15 studies presented in Table 5).

Autologous tenocyte implementation (ATI) is a novel technique that has recently been used successfully in the treatment of a rotator cuff tear and tendinopathy [47]. This was a case study documenting a single participant; thus, it may not carry much statistical power. Coupled with this, the participant had already undergone PRP, so there is the possibility that healing, at least to some extent, had already occurred. As ATI is an injection-based therapy, there is no need for surgery which would require more time out and rehabilitation; it also cancels out any chance of the repair re-tearing. As such, ATI could provide an ethical alternative, as it uses autologous tenocytes to create a healing response by utilising growth factors, interleukins, and organised collagen fibres (Schwab et al., [38]).

In 2016, Huegel et al. performed a similar, autologous tendon–derived cell therapy on rats, and also added the use of scaffold [43]. Results showed an increase in fibre organisation, cellularity, and mechanical improvements which could, to some extent, confirm results from Schwab and colleagues (Schwab et al. [38]). Interestingly, the use of autologous tendon cells could have a possible 'age effect'. Results in rats showed that it only worked in the young and old, suggesting that there needs to be an imbalance in the tendon (growing/ageing). The case study here was a 28-year-old male, which poses the question: when does ageing start to effect tendons?

Previous studies (Table 5) demonstrate that much of the research that examines human models demonstrated significant findings. However, there were no controls in five of the studies [38–41, 47], which makes comparisons difficult since they will have to be made via comparison of histological data, giving room for different methodologies and techniques to influence results. Although the findings show that shoulder function has been improved, this could suggest that no matter which engineering approached is used, shoulder function will improve.

Two of the more popular augmentation devices used were the 'GraftJacket' and the poly-L-lactic acid synthetic patch (or 'x-repair') [10, 39, 41, 42, 44]. GraftJacket worked in all but one study; however, that particular instance used rat models, whereas when used on human, it was found to significantly improve the repair. It is perhaps more established, since it has been used in surgeries since 2003 [39]. The 'GraftJacket' potentially helps increase vascularisation at the repair site through its structure and slowly dissolves once healing is complete. The poly-L-lactic acid synthetic patch unanimously found significant improvements with its use, although no control population was used, which does not rule out the possibility of extraneous factors influencing healing; it acts in tandem with the tendon whilst providing support and protection. It is not possible to say which method is better right now; more research is required including double-blinded, controlled studies. However, current findings suggest that as long as the patch can help prevent the creation of scar tissue, which causes weakness [5], then the augmentation has the chance to improve rotator cuff tear.

This is verified when evaluating research conducted on animals (Table 5), as most studies use different patches and scaffolds, but all find improvements, whether it is failure load, fibre organisation, vascularity, or even strength. Findings suggest that additional assistance to the tendon during the initial stages of healing, which prevents the accumulation of scar tissue, makes for an overall better tendon repair.

## Conclusion

Regenerative therapies have been focused on improving the healing of the rotator cuff and decreasing the chance of re-tears. Some techniques, such as PRP, have thus far been unable to present clear, concise findings and demonstrate an ability to consistently and effectively improve the repair. Stem cell research is showing positive results; however, more work is required on human patients to be able to confidently say this is the case; also, future work should look at the use of adipose MSC's as there are a few potential benefits to using these, such as a less painful sourcing and a greater total concentration of MSCs available. Overall, tissue-engineering approaches appear to be the most effective at improving healing. Future research needs to include more blinded and double-blinded controlled studies with larger population sizes to, again, be able to say that they will definitely result in an improved rotator cuff repair.

## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflict of interest.



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