



REVIEW

# Rotator cuff repair: a review of surgical techniques, animal models, and new technologies under development



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Rotator cuff tears are the most common musculoskeletal injury occurring in the shoulder. Current surgical repair fails to heal in 20% to 95% of patients, depending on age, size of the tear, smoking, time of repair, tendon quality, muscle quality, healing response, and surgical treatments. These problems are worsened by the limited healing potential of injured tendons attributed to the presence of degenerative changes and relatively poor vascularity of the cuff tendons. Development of new techniques to treat rotator cuff tears requires testing in animal models to assess safety and efficacy before clinical testing. Hence, it is important to evaluate appropriate animal models for rotator cuff research with degeneration of tendons, muscular atrophy, and fatty infiltration similar to humans. This report reviews current clinical treatments and preclinical approaches for rotator cuff tear repair. The review will focus on current clinical surgical treatments, new repair strategies under clinical and preclinical development, and will also describe different animal models available for rotator cuff research. These findings and future directions for rotator cuff tear repair will be discussed.

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More than 28 million Americans are affected by musculoskeletal injuries, costing more than \$254 billion each year.<sup>70</sup> Rotator cuff injury is the second most common musculo-

skeletal pathology after lower back pain<sup>69</sup> and the most common shoulder condition for which patients seek therapy.<sup>23</sup> In the United Kingdom, the prevalence of shoulder problems based on consultations in primary care is estimated to be 2.4%.<sup>51</sup> Between 30% and 70% of such shoulder pain is due to disorders of the rotator cuff.<sup>62</sup> More than 17 million Americans may be susceptible for shoulder impairment because of rotator cuff tendon deterioration and eventual tearing.<sup>49</sup>

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Cuff tears usually result in shoulder pain, stiffness, weakness, and loss of motion. The shoulder joint can still function with minimal pain despite a rotator cuff tear; however, limited function of the upper extremities often impairs the ability to perform basic activities. Rotator cuff disease may start as an acute tendinopathy, with progressive degeneration leading to a partial-thickness tear and eventually a complete tear.<sup>63</sup> Large tears result in disuse muscle atrophy with fatty accumulation within muscles, which may irreversibly decrease muscle function.<sup>48</sup> Failure to heal after rotator cuff repair occurs in 20% to 95% of patients and has been shown to correlate with tear size, time from injury, tendon quality, fatty atrophy, and surgical repair technique. Degenerative changes in the structure and composition of the tendons make healing very difficult.

The aim of this review is to describe the current clinical surgical treatments for rotator cuff tears, review the different animal models available for rotator cuff research, and summarize new repair approaches that are under development clinically and in preclinical studies. Although previous studies have reviewed accepted clinical treatments and preclinical models, to our knowledge, no existing review has combined both along with technologies under development.

## Rotator cuff anatomy and pathology

The rotator cuff is a group of muscles consisting of the subscapularis, supraspinatus, infraspinatus, and the teres minor.<sup>17</sup> All of these muscles are attached to the head of the humerus via their specific tendons and control the rotation and position of the arm.<sup>17</sup> The rotator cuff muscles assist shoulder motion but primarily provide stability by centering and pressing the humeral head on the glenoid<sup>17</sup> through exertion of forces in the coronal and transverse planes.<sup>66</sup> The supraspinatus and the infraspinatus contribute to glenohumeral stability in the resting position, and the subscapularis stabilizes the glenohumeral joint in the position of apprehension.<sup>17</sup>

Rotator cuff tendons respond to excessive loading by inflammation or degeneration.<sup>4</sup> This is usually manifested by pain, formation of lipids, proteoglycans, and sometimes calcified tissues in the tendon lesions, which can lead to the release of various cytokines and to adverse changes in cellular activities.<sup>50</sup> Rotator cuff tendon pathology is also influenced by the microvascular supply of rotator cuff tendons.<sup>66</sup>

Degenerative rotator cuff tears were traditionally thought to begin at the anterior part of the supraspinatus tendon, adjacent to the biceps tendon. The anterior portion was believed to transmit most of the contractile load, and because more stress would be applied daily, this tendon would be at high risk for a tear.<sup>61</sup> However, recent studies suggest that degenerative tears occur about 15 mm posterior to the biceps within the crescent at the junction of supraspinatus and infraspinatus, hence, a more posterior location.<sup>42</sup> These tears then propagate in anterior and posterior directions.<sup>39</sup>

Chronic rotator cuff tears are associated with structural changes, such as loss of muscle volume, fatty accumulation, and retraction, all of which result in muscle remodeling, subtraction of sarcomeres, and profound muscle weakness.<sup>83</sup> Progression of a tear may also lead to superior subluxation of the humeral head and, eventually, dysfunction of the shoulder. Rotator cuff tear pathology is also influenced by the microvascular supply of rotator cuff tendons.<sup>66</sup> Rotator cuff tears can also result from an acute trauma, most frequently a fall onto an outstretched arm. The supraspinatus is, again, the most commonly involved tendon; however, there is a high association with subscapularis tears.<sup>55</sup>

## Surgical treatments of rotator cuff tears

Nonoperative treatments can be used to manage most rotator cuff tears, especially in patients with lower demands. Rotator cuff tendons do not heal spontaneously, however, and surgical treatment is often required in patients who have persistent symptoms and functional impairment after conservative treatment. Operative treatment of traumatic and nontraumatic tears can be successful, with some authors reporting better results in younger patients with traumatic tears compared with degenerative tears.<sup>7</sup> Successful results were initially reported with open repair techniques using deltoid detachment and then, subsequently, through a “mini-open” deltoid split. Currently, fully arthroscopic procedures are generally considered to be the standard of care for most tears.

The superiority of arthroscopy vs open or mini-open repair is still unproven and controversial at this point (Supplementary Table S1). Overall, functional outcomes, clinical scores and retear rates are similar between arthroscopy vs mini-open repair patients. However, mini-open repair seems to be associated with more postoperative complications, and decreased short-term pain is seen with arthroscopic repair. Faster recovery, a quicker return to exercise, and better aesthetic results are other potential advantages of arthroscopic repair.

Transosseous tunnels were initially used to perform open rotator cuff repair. This technique uses sutures placed directly into bone tunnels extending from the rotator cuff footprint and exiting laterally on the tuberosity where they are tied. A limitation of this technique can be bone quality, and now, cuff repair is usually performed with suture anchors using different configurations: the single-row, the double-row, and the suture bridge repair, sometimes called the transosseous-equivalent repair technique.

The goal of using suture anchors is to restore the tendon footprint by suturing the tendon directly onto the tuberosity of the humerus. In controlled laboratory studies using cadaveric shoulders, the superior biomechanical performance of the transosseous-equivalent technique over the double-row technique and of the double-row technique over the single-row technique seems clear,<sup>14,41,56,77</sup> but this has not been translated into better clinical or functional outcomes (Sup-

plementary Table S2). The double-row repair technique does seem to improve the rate of tendon healing and to decrease re-tear rates over the single-row repair, and this could prove to be beneficial in the long-term.

## Animal models of rotator cuff repair

Animal models are a practical means to understand the cellular and molecular pathways and pathology of rotator cuff tears and to develop new technologies to improve existing treatments. Animal models of rotator cuff repair should lack spontaneous tendon healing after tendon injury. The tendon size should also allow for suture repair techniques similar to those used in humans. Ideally, irreversible muscular atrophy, stiffness, and fatty accumulation should be present after injury.<sup>15</sup> No rotator cuff tear in an animal model is identical to the human rotator cuff tear, and each model has advantages and disadvantages (Supplementary Table S3). A true rotator cuff is defined as the blending of individual flat tendons to form a single insertion. Rabbits, rats, dogs, and sheep have tendons that do not blend before inserting into the humeral head; hence, they all lack this aspect of the human rotator cuff anatomy.<sup>78</sup>

Rats have the greatest anatomic similarity to humans because of the presence of an acromial arch.<sup>15</sup> However, the acromial arch structure is somewhat different in quadrupeds: the portion of the rat supraspinatus muscle that passes under the acromial arch is muscular and not tendinous as it is in humans.<sup>24</sup> Forward arm elevation in the rat is similar to human arm abduction, and the range of motion decreases after rotator cuff tears in rats and in humans.<sup>67</sup> Rotator cuff tears in rats will also result in cartilage degeneration on the humeral head and the glenoid.<sup>46</sup> The rat is a reasonable model but has a few major differences with respect to humans. The rotator cuff tendon heals better in rats than in humans.<sup>16,52</sup> The supraspinatus provides less coverage in rats than in humans, and most of the coverage is from the subscapularis instead.<sup>52</sup> In addition, the rat supraspinatus lacks the irreversible accumulation of muscular fat and rates of failure of healing (“re-tears”) seen in humans, making it less suitable to evaluate repair techniques.<sup>16</sup> In rats, the infraspinatus tendon may be a better model to represent the human supraspinatus, because it undergoes more fat accumulation, muscular atrophy and more muscular retraction.<sup>52</sup> Even with these limitations, the rat is seen as an appropriate and cost-effective model to investigate initial safety, repair mechanisms, and efficacy of treatments, although performing surgical repairs is challenging because of its small size.<sup>15</sup>

The rabbit model is mostly used to study muscular changes, such as muscle atrophy, twitch tension (which is a single contraction in response to a brief threshold stimulation), and fatigue index (which determines energy depletion during exercise), associated with rotator cuff tears.<sup>19</sup> Atrophy and fatty accumulation occur in rabbit rotator cuff tears, as

in humans.<sup>52</sup> The rotator cuff in rabbits heals in a fashion that is similar to that of humans.<sup>30</sup> The supraspinatus and infraspinatus tendons have both been used as repair models in the rabbit, but recent studies have shown the subscapularis may be a better approximation of human pathology because it passes under an enclosed arch and fatty accumulation is prominent.<sup>19</sup> The subscapularis tendon and the scapular channel are similar in humans: both travel beneath the acromion and insert into the greater tuberosity of the humerus.<sup>24</sup> In that aspect, the rabbit’s subscapularis may be more comparable to the human supraspinatus. The rabbit is also bigger than the rat, therefore facilitating surgical models and techniques, because larger animals provide greater accuracy and reproducibility.<sup>15</sup>

The sheep infraspinatus is similar in size to the human supraspinatus.<sup>19</sup> Although the sheep infraspinatus is not intra-articular, there is still a bursa under the tendon, and the repair has some contact with the synovial fluid that lubricates the bursa.<sup>79</sup> Availability, ease of handling and housing, low cost, and acceptance to society as a research animal makes ovine models useful to study rotator cuff repair.<sup>79</sup>

Transecting the infraspinatus tendon in sheep and performing an immediate repair does not mimic the human condition; however, acute studies are suitable to assess different repair techniques or biological augmentations.<sup>68,79</sup> Animals are different than humans due to their ability to heal through tissue ingrowth and neovascularization.<sup>79</sup> In the sheep, once the infraspinatus tendon is cut from its insertion site, scar tissue can bridge the space between the tendon stump and the footprint,<sup>79</sup> although gaps at the tendon-to-bone interface are often seen,<sup>45,68</sup> and the resulting enthesis is usually reported as inferior to normal histologically and biochemically.<sup>53</sup>

In 2003, Coleman et al<sup>13</sup> developed a chronic model by covering the transected tendon end with Gore-Tex (W. L. Gore & Associates, Flagstaff, AZ, USA), which allowed for nutrient diffusion, to actively stop scar tissue formation around the stump while improving discrimination between tendon and scar tissue.<sup>13</sup> However, in chronic delayed repair, massive tendon retraction can prevent direct reattachment.<sup>13</sup> Turner et al<sup>79</sup> recommended not exceeding 4 weeks for a delayed repair. A different ovine chronic model involves releasing the infraspinatus by osteotomy and covering the bone fragment with a silicon tube.<sup>22</sup> This technique has been used to study muscle atrophy, fatty infiltration, and retraction of the musculotendinous unit<sup>59</sup> but does not approximate the human condition.

## Technologies under development for rotator cuff repair augmentation

### Extracellular tendon patches

Tendon patches are used as scaffolds for tissue ingrowth and as collagen substitutes, which should increase load to failure

and decrease stress shielding compared with injured tissue (Supplementary Table S4). Metcalf et al<sup>58</sup> used Restore (DePuy Orthopedics, West Chester, PA, USA), a small intestine submucosa scaffold deriving from a porcine source, in 12 patients during arthroscopic procedures. Two years after surgery, magnetic resonance imaging (MRI) showed thickening and incorporation of the material, but shoulder function did not improve.<sup>58</sup> Sciamberg et al<sup>75</sup> used MRI to evaluate 11 patients 6 months after implantation of Restore and revealed that 10 of 11 repairs had failed. Iannotti et al<sup>34</sup> also tested Restore in human cuff repair and found an increase in pain and inferior tendon healing.

Bond et al<sup>6</sup> tested GraftJacket (Wright Medical Arlington, TN, USA), an extracellular matrix (ECM) human cadaveric dermis scaffold, during arthroscopic rotator cuff repair in 16 patients. The overhead strength was improved, but failure was reported in 3 patients.<sup>6</sup> Burkhead et al<sup>8</sup> showed an increase tissue ingrowth into the GraftJacket patch after 2 years. Patients with arthroscopic single-row repair augmented with GraftJacket had higher American Shoulder and Elbow Surgeons and Constant shoulder scores after 24 months.<sup>2</sup> The ECM patches are used in surgery as augmentation devices but have not shown any benefit in recent randomized controlled clinical trials. Hence, further investigations are needed to prove their efficacy.

## Scaffolds

Poly(D,L-lactide-co-glycolide) (PLGA) scaffolds created by electrospinning were introduced in the infraspinatus of rabbits after a surgically induced a rotator cuff tear. An increase in bone formation at the scaffold-to-bone interface and an increase in type II collagen and proteoglycan content were observed. However, no significant difference was seen in ultimate failure load and stiffness between treated and untreated repairs.<sup>35</sup> Bone marrow stem cells (BMSCs) harvested from iliac crest of 2 rabbits during arthroscopic infraspinatus tear repair were cultured and seeded on poly-L-lactic acid scaffold, and the same scaffold without stem cells was used in contralateral shoulders. The scaffold seeded with BMSCs showed an increase in collagen type I.<sup>44</sup> Yokoya et al<sup>86</sup> used a polyglycolic acid sheet seeded with cultured autologous BMSCs in the repair of infraspinatus lesions in rabbits. After 16 weeks, collagen type I and the mechanical strength were significantly increased. Silk-collagen scaffolds seeded with tendon stem/progenitor cells increased collagen content without inducing inflammation in a rabbit rotator cuff injury model.<sup>76</sup>

This preclinical evidence can be used as a step forward in clinical translation. However, acceptable strategies for tendon pathology will require “the ideal” combination of cells and scaffolds to obtain successful outcomes. Currently the best cell/scaffold combination is unknown, and concerns exist over future availability due to regulatory constraint and cost considerations.

## Stem cells

Bone marrow-derived mesenchymal stem cells (BM-MSCs) failed to improve healing in a rat rotator cuff repair model<sup>25</sup>; however, adenoviral-mediated transduction of syngeneic BM-MSCs with the gene for membrane type 1 matrix metalloproteinase<sup>26</sup> or adenoviral-mediated scleraxis<sup>27</sup> increased fibrocartilage repair and tendon biomechanical strength. Conversely, transduction with human bone morphogenetic protein 13 had no effect.<sup>28</sup>

Drilling in the greater tuberosity while performing transosseous repair for the supraspinatus led to infiltration of the repaired tendon by BM-MSCs and increased mechanical resistance in a bone marrow chimeric rat.<sup>40</sup> Adipose tissue MSCs improved tendon healing in a rotator cuff rabbit repair model.<sup>64</sup> One clinical study harvested bone marrow mononuclear cells from the iliac crest of 14 patients during transosseous suture repair. These patients had higher University of California Los Angeles shoulder scores compared with preoperative and the MRIs showed better tendon integrity,<sup>20</sup> but this study had no control group, rendering conclusions difficult.

Few studies have used bone marrow aspirate concentrate (BMAC), which is usually taken from the iliac crest, to augment rotator cuff repair. BMAC is prepared by centrifuging bone marrow aspirate to concentrate the MSCs. Hernigou et al<sup>32</sup> injected iliac crest BMSCs aspirated during arthroscopic single-row rotator cuff repair in 45 patients, and another 45 patients underwent arthroscopic single-row repair without augmentation. At 6 months, 100% of the augmented-group had healed compared with 67% of the patients without BMAC. MRIs confirmed an increased healing rate and quality of the repaired surface with BMAC injection.<sup>32</sup> Centeno et al<sup>10</sup> reported improved function and pain scores in a multisite registry study of 102 patients, a subset of which had isolated rotator cuff tears that were treated with injections of BMAC also containing platelet-rich plasma (PRP) and platelet lysate.

Another surgical approach to draw stem cells to the repair tissue is the “crimson duvet” technique. The crimson duvet is a clot issued from bone marrow vents, which are punctured in the greater tuberosity during rotator cuff repair. The perforation has to reach the cancellous bone, letting the bone marrow flow out. Microfracture of the greater tuberosity was used in 2 clinical trials,<sup>60,65</sup> with 1 reporting greater healing in a subset of patients with larger tears.<sup>60</sup> Uthoff et al<sup>81</sup> argued that releasing BMSC from the greater tuberosity might enhance healing due to the influx of fibroblasts and vessels increasing the healing response.

## Growth factors and cytokines

Growth factors can enhance repair and enable tissue regeneration; nevertheless, further clinical investigations are required

to establish the proper timing, dosage, and delivery method. Platelet-derived growth factor (PDGF)-BB was tested in rat rotator repair cuff model, where collagen-bundle alignment the treatment group was similar to controls.<sup>85</sup> Uggen et al<sup>80</sup> used sutures coated with PDGF-BB to repair sheep infraspinatus tendon, which resulted in improved histologic properties after 6 weeks at the bone-to-tendon repair but did not change tendon strength. An infraspinatus sheep repair model showed enhanced anatomical appearance and biomechanical strength with a type 1 collagen scaffold loaded with recombinant human PDGF-BB.<sup>31</sup>

Transforming growth factor (TGF)- $\beta$ 1 and TGF- $\beta$ 3 were used in rat supraspinatus tear repair. The TGF- $\beta$ 1 group had an increase in type III collagen and a scar-mediated repair with poorer mechanical properties. However, the TGF- $\beta$ 3 group showed no difference histologically and biomechanically compared with controls.<sup>43</sup> As of now, there is still no study on rotator cuff repair using growth factors in human.

### Platelet-rich plasma

PRP has gained popularity in sports medicine and orthopedics, but its efficacy in rotator cuff tear repair is still unclear. PRP is obtained by spinning a small amount of the patient's own blood through a centrifugation process to concentrate the platelets. Several different types of PRP have been used in an attempt to augment repair. PRP can be applied as a liquid (with or without calcium-based activation before application) or implanted as a solid matrix, in which case it is called platelet-rich fibrin (PRF). PRF differs from PRP, where blood is collected without the use of any anticoagulant and is immediately centrifuged. In addition, the method of isolation will determine whether the PRP or the PRF contains leukocytes (leukocyte-PRP/PRF) or not (pure [P]-PRP/PRF), the benefits of which are currently unknown. Platelets release growth factors from the  $\alpha$ -granules and the dense granules, which contain many different cytokines and bioactive factors that have a chemotactic paracrine role and that regulate inflammation, angiogenesis, matrix synthesis, and remodeling of tissues. PRP has been postulated to improve tendon healing by increasing the concentration of growth factors and by promoting revascularization of surrounding tissues; however, results have been inconsistent in clinical trials so far.

Preclinical studies investigating PRP for rotator cuff repair are few. Most use the rat model,<sup>18,47</sup> with a few studies published in rabbits.<sup>12,84</sup> Some studies showed repair improvement with application of PRP, but others did not.

Clinical data on PRF for rotator cuff repair are more abundant (Supplementary Table S5). Leukocyte-rich PRF has been used as solid implants to attempt cuff repair augmentation by a few groups,<sup>1,87</sup> but no improvement was reported. P-PRF devoid of leukocytes has been used more

commonly, with 2 studies showing lower retear rates with P-PRF,<sup>3,9</sup> 1 study showing no difference between both groups,<sup>82</sup> and conversely, 2 studies showing more failures with P-PRF.<sup>5,73</sup> Leukocyte-rich PRP was used in 2 Level I trials, where it showed no clinical improvement but a lower retear rate<sup>71</sup> and better repair integrity<sup>29</sup> compared with the control group. Studies using P-PRP devoid of leukocytes used plateletpheresis systems<sup>36-38,54</sup> or centrifugation methods<sup>74</sup> to isolate the PRP. Four studies showed lower retear or partial retears in the P-PRP-treated group,<sup>36-38,54</sup> but 1 study showed no effect of P-PRP.<sup>74</sup>

Lower retear rates may translate into improved clinical scores at longer time points, and in that respect, treatment with PRP might eventually improve cuff repair. Assessing the efficacy of PRP from the different published studies is particularly difficult because they all vary in platelet count, single-spin vs. double-spin cycles, methods of application, growth factor concentration, leukocyte concentration, platelet activation, surgical repair, and postoperative rehabilitation. The efficacy of PRP remains an open question in orthopedic rotator cuff repair.

### Chitin and chitosan

Chitosan is a linear copolymer of  $\beta$  (1 $\rightarrow$ 4) linked D-glucosamine (GlcN) and N-acetyl-glucosamine obtained from crustacean exoskeleton by alkaline N-deacetylation of chitin. To our knowledge, only a small number of publications have used chitin and chitosan in rotator cuff repair. Funakoshi et al<sup>21</sup> used a nonwoven chitin fabric in the infraspinatus of 21 rabbits, where they observed an increase in cell number and collagen fiber alignment and enhanced structural and biomechanical properties. Melamed et al<sup>57</sup> found that rotator cuff tear repair augmented with chitosan gel enhanced healing of soft tissues. Chitosan also improved rotator cuff repair in rats by decreasing muscle fiber fibrosis and preventing muscle atrophy.<sup>72</sup>

Our laboratory has worked extensively with chitosan-glycerol phosphate/blood implants for cartilage repair applications. Nearly neutral solutions of chitosan-glycerol phosphate can be mixed with whole blood and injected over surgically prepared cartilage defects where they solidify in situ and improve marrow-stimulated cartilage repair.<sup>33</sup> We recently implemented the use of PRP combined with freeze-dried chitosan to form injectable implants for tissue repair applications. Chitosan-PRP implants resided for at least 14 days in vivo and enhanced cell recruitment to surrounding tissues compared with PRP alone. These chitosan-PRP implants were tested in a meniscus repair model, where they increased cell recruitment, vascularization, remodeling, and repair tissue integration compared with injection of PRP alone.<sup>11</sup> We are currently assessing whether these mechanisms will have similar beneficial effects in the context of rotator cuff repair.

## Conclusions

Most chronic tendon tears occur in the supraspinatus and ultimately lead to structural change such as fatty accumulation, loss of volume, muscle remodeling, subtraction of sarcomeres, and sometimes profound muscle weakness. Finding the right animal model is challenging but critically important to improve our understanding of the cellular and molecular pathways involved in rotator cuff pathology. Ultimately, such information is required to improve therapeutic treatment options. However, none of the animals have anatomy comparable to humans.

Open vs mini-open or arthroscopy does not seem to have a significant effect on clinical outcomes. The latest generation techniques involve the use of different suture configurations. Double-row configuration seems to increase the rate of tendon healing, but this has generally not translated into improved clinical and functional outcomes.

ECM patches have shown some promising findings in some animal studies, but not in randomized clinical trials. Scaffolds and cells are becoming more popular in tissue engineering as a structural support and as a cellular delivery aid, but further clinical studies are still needed. Growth factors have been shown to improve healing, but there is still no study on rotator cuff repair using growth factors in humans. One strategy would require using the ideal combination of growth factors and scaffold to complement each other.

PRP use in orthopedics is still controversial and under investigation for now, and data on its effectiveness are still limited. None of these strategies is perfectly suited for rotator cuff tear repair. One possible effective technique could be using chitosan-PRP implants. In summary, several repair strategies are available, but further clinical trials are needed to find the optimal treatment for rotator cuff repair.

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## Appendix Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.jse.2016.06.009>

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