

# Rationale for Biologic Augmentation of Rotator Cuff Repairs

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## Abstract

The structural integrity of rotator cuff repair (RCR) has been a primary focus for shoulder surgeons seeking long-term clinical and functional success. Improvements in surgical techniques have allowed for superior initial biomechanical fixation. However, tendon healing remains a significant clinical problem even after rigid time-zero repair. The lack of long-term healing has led to increased interest in biologic augmentation to improve tendon-to-bone healing. This interest has led to a rise in the investigation of small molecular therapies, cell-based strategies, and tissue-derived treatments offering surgeons a new therapeutic toolbox for potentially improving RCR long-term outcomes. However, the delivery, efficacy, and safety of these treatments remain under investigation. Additional well-designed, high-level studies are of paramount importance in creating evidence-based guidelines for the implementation of new biologic solutions. This review article discusses the current preclinical, translational, and clinical experience with and rationale for biologic augmentation in RCR.

Rotator cuff tears (RCTs) are a frequent cause of shoulder pain and disability, with approximately 98 per 100,000 people in the United States undergoing rotator cuff repair (RCR) annually, accounting for 1,360 cases per 100,000 patients seen for orthopaedic disease or injury every year.<sup>1,2</sup> The success of surgery is often determined by the eradication of pain and the return of shoulder function. When evaluating the RCR literature, whether traditional open (deltoid take down), mini-open (deltoid splitting), or arthroscopic, a high level of patient satisfaction is noted.<sup>3</sup> Surgery alleviates pain and leads to good subjective outcome scores. However, despite the resolution of pain and the improvement in subjective outcomes, a high rate of incomplete

healing or re-tearing associated with RCR surgery is noted.<sup>4</sup> Rotator cuff augmentation could be considered in patients with risk factors for failure to heal an RCR such as increasing age (mostly >65 years), multiple tendon involvement (>1), large tear size (>2 cm), retraction (>2 cm), high-grade fatty infiltration of the muscles (Goutallier >2).<sup>5-7</sup>

## Rotator Cuff Repair Failure

RCR failure should be divided into *clinical* or *mechanical* failure. Clinical failure is the subjective reporting of the patients that they are still having pain and are limited in the use of their shoulder. Mechanical failure occurs when there is a loss of fixation/repair, failure to heal, or a re-tear of the tendon. Mechanical

failure can only be detected with imaging studies. Paradoxically, the structural integrity (or lack thereof) does not necessarily correlate with the clinical outcome.<sup>8</sup> A patient may be satisfied with the surgery, but the rotator cuff tendon may remain structurally compromised. Galatz et al<sup>8</sup> raised awareness to this issue by obtaining postoperative ultrasonography in patients who had undergone repair of large and massive RCTs and reported that 94% of the repairs had “re-torn.” Since the publication of that study, the focus of many shoulder surgeons has been directed at improving the structural integrity rates. Unfortunately, the term “re-tear” does not adequately capture what may be occurring biologically and a better terminology should be used to define structural failure. Currently, the literature uses the term “re-tear,” implying that the tendon healed to the tuberosity and then tore again. It is unknown whether these are in fact repeat tears of a previously well-healed repair or whether the tendon never fully healed after attempted repair. We believe a more universal terminology of “*structural integrity rate*” may be better suited to describe the state of the tendon-bone interface.

### Importance of Rotator Cuff Integrity

Studies have shown that when the rotator cuff heals, patients have increased rotator cuff strength.<sup>9-12</sup> Harryman et al<sup>9</sup> evaluated 105 RCRs with an average age of 60 years (range, 32 to 80 years) at an average of 5 years after surgery. The authors correlated functional outcomes of patients with the integrity of the rotator cuff assessed with ultrasonography. They found that the shoulders in which the repaired cuff was intact at the time of follow-up had a better function during activities

of daily living and a better range of active flexion ( $129^\circ \pm 20^\circ$  compared with  $71^\circ \pm 41^\circ$ ) compared with the shoulders that had a large recurrent defect. The integrity of the rotator cuff at the time of follow-up, not the size of the tear at the time of repair, was the major determinant of the outcome of RCR. They also found that the quality of the rotator cuff tissue and the potential for a durable repair deteriorated with the patient's age. Nho et al<sup>10</sup> retrospectively analyzed patients in an arthroscopic rotator cuff registry who had ultrasonography documentation of cuff integrity and found that shoulders with cuff integrity at 1 year had significantly higher external rotation strength ( $P < 0.05$ ). Iannotti et al<sup>11</sup> evaluated 113 RCRs with MRI confirmation of rotator cuff integrity performed at 52 weeks after surgery; the mean ratio of the scapular abduction strength of the affected shoulder to that of the normal, contralateral shoulder was only 75% in the subjects lacking cuff integrity, whereas it was 92% in those with an intact repair ( $P = 0.0026$ ).

Boileau et al<sup>30</sup> performed arthroscopic RCR in 65 patients and later performed postoperative CT arthrogram of MRI between 6 months and 3 years. They found that patients who had a healed rotator cuff had a significantly higher Constant score (85.7 versus 78.9;  $P = 0.02$ ) and higher shoulder strength of shoulder elevation (7.3 versus 4.7 kg;  $P = 0.001$ ). In the largest study correlating the structural integrity of RCR with functional outcomes, Collin et al<sup>12</sup> reviewed the records of 210 shoulders that had a postoperative MRI at 10 years post-op and found that the total Constant score ( $P < 0.005$ ), especially the strength component ( $P < 0.001$ ), was significantly correlated to repair integrity. Based on these studies, the goal of shoulder surgeons ought to be not only improving patient's symptoms but also improving

the structural integrity rates to maximize patients' strength and function.

### Timing of Rotator Cuff Repair Failures

To better understand why RCRs fail, it is important to examine when they fail. Several studies have sequentially followed RCR with imaging studies to aid in the understanding of when RCRs fail. Miller et al<sup>13</sup> performed arthroscopic double-row repair on 22 consecutive patients with large RCTs ( $>3$  cm). The patients then underwent serial ultrasonography examinations at 2 days, 2 weeks, 6 weeks, and 3, 6, 12, and 24 months after surgery. Of the 22 arthroscopically repaired RCTs, 9 (41%) demonstrated recurrent tears. Seven re-tears of the 9 (78%) occurred within 3 months of surgery; 2 of these 7 occurred while the patient was in a sling during the postoperative period. The other 2 (22%) occurred between 3 and 6 months. No re-tears occurred after 6 months.

Similar findings were demonstrated in a multicenter, prospective, non-randomized study of a single cohort of patients by Iannotti et al.<sup>11</sup> An arthroscopic transosseous equivalent RCR was performed in 113 patients with a range of tear sizes from 1 to 4 cm. Postoperative MRIs were obtained at 2, 6, 12, 16, 26, and 52 weeks. A re-tear occurred in 19 cases of the 113 (17%). One re-tear (5%) was identified at 2 weeks, zero re-tears at 6 weeks, 7 re-tears (37%) at 12 weeks, 5 re-tears (26%) at 16 weeks, 5 re-tears (26%) at 26 weeks, and 1 re-tear (5%) at 52 weeks. The mean time to re-tear was 19.2 weeks. This number may be skewed as there were less frequent imaging intervals further out from surgery. Approximately 42% of re-tears occurred in the first 3 months and 68% occurred in the first 4 months. The authors

concluded that “rotator cuff healing is prolonged and there is an opportunity to speed healing by protecting the repair from excessive loading.”<sup>11</sup>

Hernigou et al<sup>14</sup> performed an arthroscopic single-row repair on 45 patients with tears less than 3 cm. The patients were then followed with monthly ultrasonography for the first 24 months. They found that 8 (17.8%) had a re-tear between 2 and 3 months postoperative and an additional 8 (17.8%) had a re-tear between 3 and 6 months, with an average time to re-tear at 3.4 months. What can be surmised from these studies is that the failures happen relatively early after repair, that rotator cuff healing is delayed, and can take 6 to 12 months to occur, if at all. So as surgeons, what we need to accomplish is to either strengthen the repair so the tendon stays attached to the tuberosity longer or speed up healing of the tendon before failure occurs.

### Cause of Rotator Cuff Repair Failure

Now that it is better understood *when* repairs fail, it is possible to discern *why* they fail. Early failures occur due to inadequate mechanical repair, so it is imperative to analyze where the weak link is in the repair construct. The commercially available high-strength sutures and anchors currently have superior biomechanical characteristics and have been shown not to be the mode of failure. The “weak link” is believed to be the *suture-tendon interface*.<sup>13,15</sup>

This finding has been demonstrated in several studies. Cummins et al prospectively followed 342 consecutive RCRs performed by a single surgeon.<sup>16</sup> Twenty-one (6%) subsequently required a revision RCR, with one patient undergoing two revision repairs. The mode of failure was documented at the time of

revision surgery and was found to be tendon pulling through sutures in 19 revision cases (86%). Two (9%) were re-tears adjacent to the repair site and 1 (5%) was anchor pullout.

In biomechanical testing of various RCR constructs, the most common failure is at the suture-tendon interface.<sup>17,18</sup> The reason for suture pullout is the poor tissue quality of the rotator cuff tendon. Codman suggested that degenerative changes occur in the rotator cuff tendons as we age, and the diminished biomechanical properties of the tendon may impede its ability to retain the suture. A host of histopathologic changes has been shown to occur in ruptured tendons such as collagen degeneration, disordered arrangement of collagen fibers, and greater quantities of type III collagen produced by tenocytes from ruptured tendons with a decrease in type I collagen.<sup>19</sup> In addition, a decrease in fibroblast population and the number of blood vessels occurs as the size of the rotator cuff tear increases.<sup>19</sup>

### Mechanical Augmentation to Strengthen Rotator Cuff Repair

Surgeon-controlled variables are available which can strengthen the repair (increase the load to failure) at time zero such as anchor type, suture material, knot type, stitch configuration, size and shape of a tissue-penetrating instrument, and size of the tissue bite. Anchors and high-strength sutures, regardless of manufacturer, have been maximized in their load to failure capacity. Ponce et al<sup>15</sup> evaluated stitch configuration, size and shape of a tissue-penetrating instrument, and size of the tissue bite in a laboratory setting and found that stitch configuration had the most significant increase in load to failure.

Other than stitch configuration, there are no other ways a surgeon can

improve load to failure, but we know based on the previously cited studies that the repair is still inadequate due to weakness at the tendon-suture interface. Consequently, strategies to improve RCR integrity include attempts to reinforce the native tendon by mechanical or biologic means. These approaches may involve augmenting the native tendon or enhancing the biologic healing milieu. Biologic augmentation can play a substantial role in strengthening this interface.

### Dermal Allografts

Historical reports of freeze-dried allograft tendons have shown inconsistent outcomes with some catastrophic graft failures and foreign body reactions.<sup>20</sup> In response, off-the-shelf porcine intestinal submucosal membrane “patches” rose in popularity, which unfortunately resulted in some intense local inflammatory reactions and early graft failures.<sup>21,22</sup>

A commercially available bio-inductive bovine collagen implant has also been used in RCR augmentation.<sup>23</sup> This implant is intended as an onlay over the RCR to add collagen and thicken the cuff and does not provide any mechanical support or advantage. To date, the only clinical report is for the repair of partial-thickness tears.

Dermal allografts, otherwise known as acellular dermal matrices (ADMs), have been the subject of extensive clinical and preclinical evaluation and can significantly increase the ultimate load to failure. These grafts are processed to remove donor cells, leaving behind the extracellular matrix, which is mostly composed of type I collagen. There are several commercially available ADMs with different methods of processing and sterilization, as well as handling characteristics.<sup>24</sup> Given their biomechanically proven superior

suture pullout strength,<sup>25,26</sup> ADMs function to strengthening the repair while allowing an optimized environment for host cells and growth factors to promote repair site healing.

Multiple biomechanical studies have evaluated ADMs in rotator cuff repair model.<sup>17,26,27</sup> Barber et al<sup>17</sup> demonstrated in a cadaver RCT model an increase in mean failure strength in augmented repairs with ADMs (325 Newtons) compared with cadaveric controls (273 Newtons) ( $P = 0.047$ ). Beitzel et al<sup>27</sup> evaluated ADM augmentation in a cadaver RCR model and found a statistically significant increase in load to failure in ADM-augmented repairs versus non-augmented controls (575.8 N versus 348.9 N;  $P = 0.025$ ).

These biomechanical findings have been supported clinically. A level 2, prospective, randomized controlled study by Barber et al<sup>18</sup> evaluated 42 patients with >3 cm, two-tendon RCTs repaired arthroscopically. Twenty-two patients were randomized to single-row arthroscopic repair and 20 patients to single-row arthroscopic repair augmented by ADMs by an onlay technique as described by Labbe.<sup>28</sup> At an average follow-up of 24 months, 85% of the augmented repairs were intact on MRI at follow-up, compared with 40% in the control group ( $P < 0.05$ ). Agrawal retrospectively reviewed 14 patients with either RCTs greater than 3 cm or recurrent RCTs (may be less than 3 cm) that were arthroscopically repaired with a double-row technique with ADM augmentation. Postoperative MRI obtained at an average of 16.8 months revealed 85.7% of repairs to be intact, with 14.3% having recurrent tears of less than 1 cm.<sup>29</sup> These clinical studies demonstrate that RCRs augmented with ADMs appear to have a much higher rate of structural integrity on postoperative imaging compared with what has been previously reported in the literature.<sup>11,30,31</sup>

### Enhancing the Biologic Healing of Rotator Cuff Repair

Extensive research and investigations are underway to improve the second component of RCR: tendon-to-bone healing.

### Marrow Venting Procedures (Microfracture)

Microfracture of the greater tuberosity was popularized by Snyder and Burns<sup>32</sup> who coined the term “crimson duvet” for the bed of bloody fluid blanketing the greater tuberosity after microfracturing allows the bone marrow elements (mesenchymal stem cell [MSC], platelets, growth factors) to surface.

Dierckman et al<sup>33</sup> retrospectively reviewed 52 patients (53 shoulders) who underwent a single-row RCR of tears between 2 and 4 cm with marrow stimulation. At a minimum follow-up of 24 months, MRI revealed rotator cuff healing in 48 of 53 shoulders (91%). The limitation of this study was the absence of a control group. Milano et al,<sup>34</sup> in a prospective, randomized study, compared 40 control subjects with 40 patients who had a microfracture in conjunction with RCR. Overall, the structural integrity rate was 52.6% in the control group and 65.7% in the venting group, without a significant difference between the groups ( $P = 0.256$ ). However, a subgroup analysis by tendon size showed that for large tears, the microfracture group had a higher structural integrity rate compared with the control group (60% (6 of 10) versus 12% (1 of 8), respectively;  $P = 0.04$ ). Although this subgroup analysis may be underpowered, the findings have been substantiated by Taniguchi et al<sup>35</sup> who followed 44 control subjects and 67 vented arthroscopic RCR by a single surgeon with a minimum 12-month follow-up

with MRI. No difference was noted in the structural integrity rates between the control group and vented group for medium-sized tears (81.2% versus 86.4%, respectively;  $P = 0.62$ ). However, a significant improvement occurred in the structural integrity rates for large to massive tears between the control group and vented group (71.4% versus 95.5% respectively;  $P = 0.025$ ). Osti et al<sup>36</sup> conducted a prospective, randomized trial with 29 controls and 28 vented during arthroscopic RCR. Although a significant difference existed in functional outcome and pain scores for the vented group at 3 months, this difference did not carry through at the final follow-up (minimum 2 years). Furthermore, postoperative MRI performed at the final follow-up showed no difference in the structural integrity rates between the groups (89.7% versus 92.9%, respectively;  $P = 0.67$ ). One of the limitations of this study was that the authors do not report the size of the RCT, and as elucidated by the previous study, there may be a difference in healing rates in larger tears.

Based on these studies, microfracture (venting) at the RCR site may be beneficial in improving healing rates or large and massive tears but do not play a role for small- and medium-sized tears.

### Platelet-Rich Plasma

Platelet-rich plasma (PRP) is an autologous concentrate of a patient's own blood that is injected into or onto the injured soft tissue in an effort to promote a healing response. The release of growth factors from platelet alpha-granules enhances cell proliferation of tenocytes and promotes the synthesis of extracellular matrix cell proliferation, chemotaxis, cell differentiation, and angiogenesis to enhance the healing process.<sup>37</sup> The literature has been inconsistent on the

outcomes of PRP use in RCR. Several studies have demonstrated that although PRP had no effect on the clinical outcomes after RCR, it did have an impact on the structural integrity, suggesting that PRP promotes tendon healing to bone. Other studies have shown that it did not have an effect on the structural integrity rate.<sup>38-40</sup> Vavken et al<sup>38</sup> in a meta-analysis of 13 published reports between 2010 and 2014 found that for small- and medium-sized tears (<3 cm), the risk ratio for re-tear was 0.60, consistent with a significant difference in favor of PRP use ( $P = 0.038$ ). Warth et al<sup>39</sup> in a meta-analysis and meta-regression analysis of eight level I and II studies found that if the RCT size was greater than 3 cm in AP length, the PRP-treated group exhibited decreased re-tear rates after double-row repairs (25.9% versus 57.1%, respectively;  $P = 0.046$ ). Cai et al<sup>40</sup> in a meta-analysis of five level I studies found that although no statistically significant differences existed between groups in the overall outcome scores ( $P > 0.05$ ), there were better healing rates in patients treated with PRP ( $P < 0.03$ ) who had small/moderate full-thickness tears.

One of the main reasons for the inconsistency in the literature is that not all PRP is the same with regard to the concentration, content, preparation method, and delivery technique. There are various commercially available systems that produce different concentrations of PRP compared with normal levels.<sup>41</sup> In the same patient, there can be a high degree of variability in platelet concentration throughout the day. Other factors such as activation of platelets to create a gel or clot, as well as the number of white blood cells, can have an effect on the healing potential and inconsistency in the findings.

A recent meta-analysis by Hurley et al<sup>42</sup> of 18 randomized controlled

trials including 1,147 patients analyzed separately the effect of PRP and platelet-rich fibrin (PRF) on RCR. PRF is clotted after it is collected, is immediately activated, and is sutured at the bone-tendon interface. The authors found no difference in healing rates between PRF and controls, as well as patient satisfaction, Constant score, and American Shoulder and Elbow Surgeons score. However, they found that PRP improved the structural integrity rates compared with the controls overall (82.8% versus 69.5%;  $P < 0.05$ ), small to medium tears (77.6% versus 61.75;  $P < 0.05$ ), and medium to large tears (93.3% versus 73.5%;  $P < 0.05$ ). In addition, PRP use leads to significantly improved visual analog scale at 30 days and at the final follow-up, as well as improved Constant and UCLA scores but no difference in American Shoulder and Elbow Surgeons scores. More importantly, the authors were able to differentiate between leukocyte-rich and leukocyte-poor PRP formulations and found that the leukocyte-poor formulations had significant improvement in healing rates compared with controls (83% versus 69.1%, respectively;  $P < 0.05$ ), whereas the leukocyte-rich formulations did not (69.5% versus 59.3%;  $P = 0.36$ ). A summary of all level I studies with PRP used in rotator cuff repair is shown in Table 1.

### Mesenchymal Stem Cells

Currently, two autologous sources of stem cells are available which can be commercially used: adipose-derived stem cells and bone marrow concentrate (BMC).<sup>56</sup> Both can be harvested, prepared, and then reinjected in an in-office setting with minimal donor site morbidity.

As for PRP, a high variability exists in the concentration on progenitor cells that is dependent on the age of the donor, location of the harvest,

and preparation method. BMC has been used for decades in Europe with a long-term follow-up study detailed later which shows significant benefit in RCR surgery, and until only recently, there have been no studies on the use of adipose-derived stem cells in RCR surgery.<sup>14,42</sup>

### Bone Marrow Concentrate

Hernigou et al<sup>14</sup> performed an arthroscopic single-row repair on 45 matched pair patients with tears less than 3 cm. The treatment group received BMC at the time of the repair, whereas the control group did not (nonrandomized). The patients were matched for age, sex, dominance, and tear size. The patients were then followed clinically and with imaging studies. Monthly ultrasonography was performed for the first 24 months. MRIs were performed at 3, 6, 12, and 24 months, and 10 years postoperatively. The authors found that bone marrow-derived MSC injection during RCR enhanced the healing rate and improved the quality of the repaired surface. All 45 pairs (100%) with MSC augmentation had healed by 6 months, compared with just 30 of 45 non-MSC repairs (67%). BMC injection was also protective against rupture through the most recent follow-up (10 years postoperatively). At this time point, 87% of patients in the MSC-treated group had intact cuffs, but just 44% were intact in the unaugmented group. A greater number of transplanted MSCs also appeared to propagate tissue integrity as those with cuff tears at any time during the follow-up had received fewer MSCs compared with those who maintained a successful repair. Another significant finding in this study was that no re-tears were present in patients who received BMC MSC in the first 6 months after surgery. It is important to highlight

Table 1

## Level 1 Studies With a Minimum of 12-Month Follow-up

Type of PRP	Study (Year)	Treatment Group (n)	Control Group (n)	Follow-Up	Differences in Re-tear/Healing Rates	Second Look or Imaging	Functional Scores	Conclusion
PRP								
Leukocyte poor	Ebert et al <sup>43</sup> (2017)	27	28	42	No	MRI—no differences.	CS, OSS, ASES, qDASH, GRC. The only difference was that the PRP group had better strength CS subscale.	Significant postoperative clinical improvements and high levels of patient satisfaction were observed in patients at midterm after supraspinatus repair. Although pain free, maximal abduction strength was greater in the midterm after PRP treatment; repeated applications of PRP delivered at 7 and 14 days after surgery provided no additional benefit to tendon integrity.
	Flury et al <sup>44</sup> (2016)	60	60	24	No	US and MRI—PRP re-tear rate lower, 12.2% vs 20.8%.	CS, OSS, pASES, qDASH, EQ5D. Pain level—no differences.	A single intraoperative injection of pure PRP on the reconstructed footprint of the supraspinatus tendon showed no significant effect on the clinical and patient-reported outcomes up to 24 months after arthroscopic rotator cuff repair compared with an intraoperative injection of ropivacaine within the subacromial space. However, a similar time-limited, pain-reducing effect was noted between the two treatments. It remains unclear whether an improvement in patient outcomes, notably in nonsmoking patients, can be achieved with locally administered growth factors in the form of pure PRP.
	Pandey et al <sup>45</sup> (2016)	52	50	12	Yes	Doppler US—vascularity in the PRP group repair site at 3 months ( $P < 0.05$ ) and in peribursal tissue until 12 months.	CS, UCLA, ASES, VAS—VAS sign. Better until 6 months; UCLA better at 6 and 12 months and CS at 12 and 24 months for PRP.	Superior structural healing of arthroscopic repair of the large rotator cuff tear with a single-row technique when treated by moderately concentrated PRP compared with controls. PRP was also seen to accelerate the vascularity of the rotator cuff and the surrounding tissues in the early phase. PRP is beneficial in reducing the re-tear of large tears.

(continued)

ASES, American Shoulder and Elbow Surgeons; CS, Constant score; GRC, Global Rating of Change; MRI, magnetic resonance imaging; OSS, Oxford Shoulder Score; pASES, patient American Shoulder and Elbow Surgeons; PRP, platelet-rich plasma; quick DASH, EQ5D, EuroQol 5 Dimensions; SER, strength in external rotation; SPADI, Shoulder Pain and Disability Index; SST, Simple Shoulder Test; SSV, subjective shoulder value; UCLA, University of California–Los Angeles, VAS = visual analog scale.

**Table 1 (continued)**

Level 1 Studies With a Minimum of 12-Month Follow-up								
Type of PRP	Study (Year)	Treatment Group (n)	Control Group (n)	Follow-Up	Differences in Re-tear/Healing Rates	Second Look or Imaging	Functional Scores	Conclusion
	Jo et al <sup>46</sup> (2015)	37	37	12	Yes	MRI—PRP re-tear rate lower 3% vs 20%. Better cross-sectional area in the PRP group.	CS, UCLA, ASES, VAS, SPADI, SST—comparable, except VAS worst pain.	Compared with repairs without PRP augmentation, the current PRP preparation and application methods for medium to large rotator cuff repairs significantly improved the quality, as evidenced by a decreased re-tear rate and increased CSA of the supraspinatus but not the speed of healing.
	Malavolta et al <sup>47</sup> (2014)	27	27	24	No	MRI—no differences.	CS, UCLA, ASES, VAS—the only significant difference was UCLA at 12 months.	PRP prepared by apheresis and applied in the liquid state with thrombin did not promote better clinical results at 24-month follow-up. Given the numbers available for the analysis, the re-tear rate also did not change.
	Ruiz-Moneo et al <sup>48</sup> (2013)	32	31	12	No	MRI—no differences.	UCLA, patient satisfaction—no differences.	No differences in rotator cuff healing or improvements in function were observed in the 1-year postsurgical clinical and radiologic follow-up assessments.
	Jo et al <sup>49</sup> (2013)	24	24	12	Yes	MRI or CT—PRP re-tear rate lower, 20% vs 55.6%. Better cross-sectional area in the PRP group.	CS, UCLA, ASES, VAS, SPADI, SST—comparable, except for overall function ( $P = 0.043$ ).	The application of PRP for large to massive rotator cuff repairs significantly improved structural outcomes, as evidenced by a decreased re-tear rate and increased CSA of the supraspinatus compared with repairs without PRP augmentation. Although no significant difference existed in clinical outcomes, except the overall shoulder function after 1-year follow-up, better structural outcomes in the PRP group might suggest improved clinical outcomes at longer-term follow-up.
Leukocyte rich	Zhang et al <sup>50</sup> (2016)	30	30	12	Yes	MRI—PRP re-tear rate lower, 13% vs 30%.	CS, UCLA, DASH VAS, ROM—no differences.	The local injection of PRP into a primary arthroscopic double-row cuff repair resulted in lower recurrence rates than repairs without the novel biologic augmentation material.

(continued)

ASES, American Shoulder and Elbow Surgeons; CS, Constant score; GRC, Global Rating of Change; MRI, magnetic resonance imaging; OSS, Oxford Shoulder Score; pASES, patient American Shoulder and Elbow Surgeons; PRP, platelet-rich plasma; quick DASH, EQ5D, EuroQol 5 Dimensions; SER, strength in external rotation; SPADI, Shoulder Pain and Disability Index; SST, Simple Shoulder Test; SSV, subjective shoulder value; UCLA, University of California—Los Angeles, VAS = visual analog scale.

Table 1 (continued)

Level 1 Studies With a Minimum of 12-Month Follow-up								
Type of PRP	Study (Year)	Treatment Group (n)	Control Group (n)	Follow-Up	Differences in Re-tear/Healing Rates	Second Look or Imaging	Functional Scores	Conclusion
	Randelli et al <sup>51</sup> (2011)	26	27	24	No	MRI—no differences.	CS, UCLA, VAS, SST SER—better at 3 months for PRP. Comparable at 6, 12, and 24 months.	The results of our study showed autologous PRP reduced pain in the first postoperative months. The long-term results of subgroups of grade 1 and 2 tears suggest that PRP positively affected cuff rotator healing.
Platelet-rich fibrin								
Leukocyte poor	Weber et al <sup>52</sup> (2013)	30	30	12	No	MRI—no differences.	UCLA, VAS, SST, ROM—no differences.	Platelet-rich fibrin matrix was not shown to significantly improve perioperative morbidity, clinical outcomes, or structural integrity. Although longer-term follow-up or different PRP formulations may show differences, early follow-up does not show significant improvement in perioperative morbidity, structural integrity, or clinical outcome.
	Castricini et al <sup>53</sup> (2011)	43	45	20.2	No	MRI—no differences.	CS—no differences.	This study does not support the use of autologous PRFM for augmentation of a double-row repair of a small or medium rotator cuff tear to improve the healing of the rotator cuff. Given the heterogeneity of PRFM preparation products available in the market, it is possible that other preparations may be more effective.
	Zumstein et al <sup>54</sup> (2016)	17	18	12	No	MRI—no differences.	SSV, CS, VAS, SST, ROM—no differences.	Arthroscopic rotator cuff repair with the application of L-PRF yielded no beneficial effect on clinical outcome, anatomic healing rate, mean postoperative defect size, and tendon quality at 12 months of follow-up.
Leukocyte rich	Gumina et al <sup>55</sup> (2012)	39	37	13	Yes	MRI—no re-tears in the PRP group vs 8%.	CS—no differences.	The use of the platelet-leukocyte membrane in the treatment of rotator cuff tears improved repair integrity compared with repair without a membrane. However, the improvement in repair integrity was not associated with greater improvement in the functional outcome.

ASES, American Shoulder and Elbow Surgeons; CS, Constant score; GRC, Global Rating of Change; MRI, magnetic resonance imaging; OSS, Oxford Shoulder Score; pASES, patient American Shoulder and Elbow Surgeons; PRP, platelet-rich plasma; quick DASH, EQ5D, EuroQol 5 Dimensions; SER, strength in external rotation; SPADI, Shoulder Pain and Disability Index; SST, Simple Shoulder Test; SSV, subjective shoulder value; UCLA, University of California—Los Angeles, VAS = visual analog scale.



that the authors examined the cells only in a quantitative fashion and that the standard criteria from the International Society for Cellular Therapy were not tested to designate a cell population as “MSCs”: (1) culture-expanded cells that adhere to tissue culture plastic; (2) cells that retain the capability for tri-lineage differentiation (bone, cartilage, and adipose); (3) cells expressing CD105, CD73, and CD90 (with 95% prevalence); and (4) cells lacking expression of CD45, CD34, CD14 or CD11b, CD79 alpha or CD19, and HLA-DR surface molecules.<sup>57</sup>

Ellera Gomez et al<sup>58</sup> reported similar results to those of Hernigou et al in a small case series of 14 patients treated with BMC injection during mini-open RCR. Although this study lacked a control group for adequate comparison, 13 of the 14 patients had substantial clinical improvement at 1-year follow-up and all tendons were confirmed intact by MRI. In summary, there are only two studies with limited scientific rigor which does not allow for a strong conclusion in regard to BMC use in rotator cuff surgery.

### Adipose-Derived Stem Cells

Kim et al<sup>59</sup> published the first clinical results of adipose-derived stem cells as an augment to rotator cuff surgery in a case-control series of 35 patients undergoing arthroscopic repair. Patients matched for age, sex, and tear size were followed for a minimum of 12 months postoperatively. The authors found no difference at the final follow-up in regard to the range of motion, pain, or functional outcomes measures. However, the structural integrity of the tendon as indicated by MRI proved to be significantly better in the adipose-derived stem cell-treated group, with only 14.3% tears (5 of the 35)

compared with 28.5% (10 of the 35) in the conventional group ( $P < 0.001$ ). Of note, all available data on ADSC have been reported on this single study, and thus, the results should be considered experimental. Additional randomized, prospective studies are needed to determine the efficacy of this treatment.

The aforementioned studies of biologic therapies for RCR have focused on improving healing at the bone-tendon interface. Conversely, the treatment of muscle atrophy and fibroadipogenic degeneration observed in the setting of large tears has largely been ignored. This is despite the fact that both atrophy and degeneration have been correlated with poor functional outcome and decreased strength after RCR<sup>60</sup> and have been shown to be largely irreversible even in the setting of complete tendon-to-bone healing.<sup>61</sup> This has prompted an investigation into the use of both bone marrow and adipose-derived stem cells to regenerate injured rotator cuff muscle.<sup>62,63</sup> In a recent study by Eliasberg et al,<sup>62</sup> a local injection of adipose-derived human perivascular stem cells was shown to diminish muscle atrophy and fibroadipogenic degeneration in a small animal model of massive RCT. The authors suggest that these cells act as both regenerative precursors and a source of paracrine growth factors to stimulate local satellite cell activity.<sup>62</sup> Further large animal preclinical and human clinical studies are necessary to determine the effectiveness of myo-regeneration on improving both rotator cuff healing and ultimate functional outcome.

### Summary

Although patients do well clinically after RCR surgery, mechanical failure of the repair can be as high as 94% in massive tears. Failures can

occur early at the suture-tendon interface or later due to delayed healing of the rotator cuff. The suture-tendon interface can be augmented with dermal allografts (ADMs), and healing of the tendon can be expedited with biologics. Biologic augmentation has the potential to improve tendon healing after RCR, but additional high-level studies are needed to translate preclinical findings into clinical applications.

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