Biologics for Rotator Cuff Repair

A Critical Analysis Review

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Abstract

» The complexity of tendon to bone healing in a rotator cuff surgical procedure has led to the investigation of biologic augmentation such as platelet-rich plasma, stem cells, and biomaterials to enhance the healing environment and to decrease the prevalence of failure.

» Among the many types of biologic augmentation, there is considerable heterogeneity of the content, quality, and quantity of growth factors used in platelet-rich plasma and bone marrow aspirate concentrate, and conclusions from individual studies may not necessarily be generalizable to other formulations within the group.

» Current Level-I evidence suggests that universal use of platelet-rich plasma provides no significant clinical benefit in rotator cuff repair.

» Although some evidence exists for the use of stem cells from bone marrow aspirate concentrate and the use of biologic grafts, results from Level-I studies are lacking.

» Level-I trials focused on the evaluation of clinical outcomes (i.e., American Shoulder and Elbow Surgeons [ASES] score, University of California at Los Angeles [UCLA] shoulder score, Constant score, Simple Shoulder Test) should be performed to help to determine the appropriate use of biologic augmentation in rotator cuff surgical procedures.

Rotator cuff tears are a common cause of pain and disability of the shoulder. Despite an increase in the number of operations performed and enhanced surgical techniques, unacceptably high rates of failure of up to 94% still occur[1]. Although the causes of failure are multifactorial, research over the past couple of decades has focused on approaches to improve the healing environment through the addition of growth factors in the form of platelet-rich plasma, stem cells, and biologic scaffolding such as interposition or augmentation grafts. The potential impact of these biologic agents must be evaluated with evidence from high-quality studies. The aim of this review was to provide an evidence-based summary of the biologic augmentation options available for use by the orthopaedic surgeon performing rotator cuff repair and to identify areas where further research is warranted.

A search of PubMed, Embase, CINAHL, and Cochrane Central Register of Controlled Trials (CENTRAL) databases was performed in September 2017. Search terms of "rotator cuff tear," "platelet rich plasma," "mesenchymal stem cell," "bone marrow aspirate," "adipose derived stem cell," and "allograft" were used, as appropriate, along with synonyms and filters for

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humans, English language, research or clinical research papers, and peer-reviewed research journals. Abstracts were screened and relevant manuscripts were reviewed. The best available Level of Evidence was included for each platelet-rich plasma, stem cell therapy, and biologic graft intervention in combination with rotator cuff repair and outcomes reporting the assessment of both clinical and structural integrity of the repair. Manuscripts included in the platelet-rich plasma or stem cell therapy review were required to include experimental groups (platelet-rich plasma or stem cell treatment) and a control group without platelet-rich plasma or mesenchymal stem cell-containing therapy. To be included in the review of biologic grafts, patients with large or massive rotator cuff tears that underwent repair with a graft were compared with a control group that included at least a partial primary repair or full primary repair under tension without the use of a graft. Additional articles were found by reviewing citations of relevant manuscripts. Exclusion criteria included case reports, pilot studies, unpublished manuscripts, editorials, manuscripts without available full text, studies in which the surgical technique was unclear or using tendon transfers, or studies in which clinical outcomes or structural integrity of repair were not reported.

Biology of Rotator Cuff Healing

The rotator cuff tendons are primarily composed of type-I collagen with a decreasing blood supply from medially to laterally as the tendon inserts on the proximal part of the humerus in a transition of 4 distinct zones: tendon, nonmineralized fibrocartilage, mineralized fibrocartilage, and bone[2,3]. In the complex process of rotator cuff tendon to bone healing, there are 3 overlapping stages that utilize different cell mediators[4]. The first stage, from 0 to 7 days, is the inflammatory phase and is characterized by fibrin and fibronectin deposition by platelets. Macrophages and neutrophils are recruited by insulin-like growth factor-1, platelet-derived growth factor, and transforming growth factor-beta (TGF-β) that are secreted by platelets, leading to the initiation of the inflammatory cascade that also includes the cytokines' interleukin-1-beta (IL-1β) and tumor necrosis factor alpha (TNF-α)[4]. These factors activate nuclear factor kappa B (NF-κB), which is involved in apoptosis of muscle fibers and tenocytes and inhibits the regeneration pathway[4]. Once the cellular debris has been removed, there is a transition to the fibroblastic repair stage characterized by transformation of monocytes to support the environment for new tissue formation[4]. In the rotator cuff muscle, anti-inflammatory macrophages express myogenic regulatory factors to help to develop myocytes from precursor cells. Concurrently, these anti-inflammatory macrophages secrete TGF-β1, which leads to the production of structurally inferior fibrovascular scar tissue consisting of type-III collagen at the tendon-bone interface[5]. Lastly, the remodeling phase is characterized by increasing amounts of type-I collagen, believed to be produced by tenocytes and undifferentiated mesenchymal stem cells, and a reduction of less-organized, scar-like type-III collagen[3,6]. The complex interactions of the numerous cytokines and growth factors involved in the healing process can ultimately lead to the success or failure of the repair by enhancing the regeneration pathway and limiting the degradation pathway.

Platelet-Rich Plasma

Platelet-rich plasma is a concentrate derived from autologous blood that has been centrifuged to separate out platelets that contain growth factors and cytokines (Table I) from other components of whole blood[7,8]. The concentration of platelets as well as the formulation of platelet-rich plasma, including the presence or absence of leukocytes, is variable and dependent on the technique of centrifugation. Platelet-rich plasma can also be activated through the initiation of 2 processes: (1) immediate-release growth factors from alpha-granules, and (2) fibrinogen cleavage to initiate a clotting process allowing the formation of a semi-solid or solid platelet matrix that confines the growth factors to a chosen site[9]. The product formed by the activation of platelet-rich plasma to create a solid fibrin matrix is often referred to as platelet-rich fibrin matrices, but this vernacular does not describe the composition of the platelet-rich plasma itself. Leukocyte-rich, platelet-rich plasma retains leukocytes, namely neutrophils, and has pro-inflammatory effects[10], and leukocyte-poor, platelet-rich plasma has the neutrophils removed and is anti-inflammatory[11,12].

TABLE I Growth Factors in Platelet-Rich Plasma[7,8]

Growth Factor	Source	Function
Platelet-derived growth factor	Platelets	Mitogenic for tendon fibroblasts and chondrocytes; stimulates angiogenesis
Vascular endothelial growth factor	Platelets	Stimulates angiogenesis
TGF-β1	Platelets	Regulates fibrosis and myocyte regeneration
Fibroblast growth factor	Platelets	Controls cell growth, proliferation, differentiation, and apoptosis
Epithelial growth factor	Platelets	Stimulates epidermal and dermal proliferation
Hepatocyte growth factor	Plasma	Angiogenesis, mitogen for endothelial cells, antifibrotic
Insulin-like growth factor-1	Plasma	Mediator of growth hormone-stimulated growth of myoblasts and fibroblasts

TABLE II Four Categories of Platelet-Rich Formulations Based on Leukocyte and Fibrin Concentrations[17,18]

Platelet-Rich Plasma Type	Leukocytes	Fibrin Content	Final Matrix	Platelet Concentrate Brands or Technique	Platelet Concentration
Leukocyte-rich, platelet-rich plasma	Increased	Decreased	Liquid or gel	Biomet GPS III (Biomet); Harvest Smart-PreP (Harvest Technologies)	3 to 8 times
Leukocyte-poor, platelet-rich plasma	Decreased	Decreased	Liquid or gel	Vivostat (Vivostat A/S)	3 to 9 times
Leukocyte-rich, platelet-rich fibrin matrices	Increased	Increased	Solid gel	Choukroun technique	1.4 to 4.9 times
Leukocyte-poor, platelet-rich fibrin matrices	Decreased	Increased	Solid gel	Fibrinet (Cascade Medical)	1 to 1.5 times

Many of the cytokines that are found at the site of enthesis healing have been demonstrated to also exist in high concentrations in platelet-rich plasma[13-16]. As a result, platelet-rich plasma has been a popular target of investigation in the hopes of identifying a biologic treatment that will create an environment that is conducive to healing. Numerous well-designed, prospective randomized trials have been performed attempting to find a beneficial effect of platelet-rich plasma in rotator cuff repair. Unfortunately, the true composition of the platelet-rich plasma that is being delivered is often unknown (unknown platelet-rich plasma), and one must always consider the methods of preparation to determine if leukocyte-rich, platelet-rich plasma or leukocyte-poor, platelet-rich plasma, or if activated (platelet-rich fibrin matrices) or non-activated (liquid), platelet-rich plasma was delivered. Platelet-rich fibrin matrices can also be leukocyte-rich or poor. Table II[17,18] summarizes the categories of the different types of platelet-rich plasma.

When evaluating the highest Level of Evidence and considering only well-designed, prospective randomized trials together, there is little evidence that leukocyte-poor, platelet-rich plasma improves the clinical outcome scores or re-tear rate[11,12,19-23] at >6 months following rotator cuff repair. However, there are several studies that would support the use of leukocyte-poor, platelet-rich plasma to reduce recurrent tear rates. Jo et al.[24] demonstrated a significant reduction in re-tear rates in rotator cuff tears >3 cm when repaired with a double-row technique using leukocyte-poor, platelet-rich plasma with a mean (and standard deviation) of $1{,}096.48 \pm 255.40 \times 10^3$ platelets/μL ($p = 0.023$). In a separate study, Jo et al.[25] utilized activated leukocyte-poor platelet-rich plasma with a mean of $1{,}218 \times 10^3$ platelets/μL inserted at the bone tendon interface and reported a reduced recurrent tear rate (3%) when compared with patients randomized to repair without leukocyte-poor, platelet-rich plasma (20%) ($p = 0.032$) and improved the cross-sectional area of supraspinatus seen after the repair of medium to large tears using a double-row repair technique. Additionally, Pandey et al.[26] utilized non-activated, leukocyte-poor, platelet-rich plasma with a mean of 474×10^3/μL platelets and demonstrated via ultrasound a decreased re-tear rate in favor of the leukocyte-poor, platelet-rich plasma (3.8% compared with 20%; $p = 0.01$) of large tears (3 to 5 cm) undergoing a single-row repair.

The use of leukocyte-rich, platelet-rich plasma preparations exhibited a similar lack of significant effect on clinical outcome scores and re-tear rates >6 months after repair[27-30]. However, in 1 study, Gumina et al.[31] found that the use of activated, leukocyte-rich, platelet-rich plasma improved repair integrity (no re-tears in the leukocyte-rich, platelet-rich plasma group compared with 3 in the control group; $p = 0.04$) but acknowledged that it was not associated with greater improvement in the functional outcome scores. In addition, there have been multiple studies using unknown platelet-rich plasma[32-34] that have also demonstrated no significant effect on clinical outcomes or re-tear rates; however, these studies are difficult to interpret, as the platelet-rich plasma formulation was not disclosed.

When critiquing the results of platelet-rich plasma studies, it is important to recognize that the concentrations and makeup of platelet-rich plasma formulations are not all standardized and often are not reported, in part because of proprietary limitations. Therefore, the results for 1 preparation and study design may not be generalizable. In addition, levels of growth factors in platelet-rich plasma have been reported to vary widely in preparations made in a similar fashion. Study design, size of tears, surgical techniques (single row compared with double row), and composition of platelet-rich plasma also vary widely among the platelet-rich plasma literature, making comparison difficult (Table III)[11,12,19,21,24-28,30-32,34].

Despite this heterogeneity of the literature, several meta-analyses with differing inclusion criteria have been performed. In a systematic review of 7 meta-analyses evaluating platelet-rich plasma of all formulations[35], no improvement in clinical outcome scores or recurrent tear rates were found. However, subgroup analysis performed

TABLE III Clinical Outcome Scores and Radiographic Results of Level-I Prospective Randomized Trials with ≥1-Year Follow-up

Study	Type of Platelet-Rich Plasma	No. of Patients	Follow-up *(mo)*	Postoperative Outcome Score *(points)*		Imaging Method	Tear Size *(cm)*	Repair Intervention	Intact Repairs	
				Control	Platelet-Rich Plasma				Control	Platelet-Rich Plasma
Castricini[32] (2011)	Platelet-rich fibrin matrix, unknown	88	16	88.4 (Constant)	88.4 (Constant)	MRI	0 to 3	Double-row	34 of 38	39 of 40
Gumina[31] (2012)	Leukocyte-poor, platelet-rich fibrin matrix	76	12	10.1 (Simple Shoulder Test)	10.5 (Simple Shoulder Test)	MRI	2 to 4	Single-row	34 of 37	39 of 39*
Jo[24] (2013)	Leukocyte-poor, platelet-rich plasma	38	12	69.8 (Constant)	74.8 (Constant)	MRI or CT arthrogram	>3	Double-row	8 of 18	16 of 20*
Randelli[27] (2011)	Leukocyte-rich, platelet-rich plasma	45	24	75.7 (Constant)	78.3 (Constant)	MRI	>0	Single-row	11 of 23	13 of 22
Ruiz-Moneo[11] (2013)	Leukocyte-poor, platelet-rich plasma	63	12	23.8 (UCLA)	23.2 (UCLA)	MRI	>0	Double-row	17 of 28	19 of 32
Weber[19] (2013)	Leukocyte-poor platelet-rich fibrin matrix	59	12	29.6 (UCLA)	27.9* (UCLA)	MRI	>0	Single-row	17 of 24	16 of 28
Ebert[21] (2017)	Leukocyte-poor platelet-rich plasma	60	42	85.2 (Constant)	86.2 (Constant)	MRI	0 to 2	Double-row	27 of 28	27 of 27
Pandey[26] (2016)	Leukocyte-poor platelet-rich plasma	102	24	87.6 (Constant)	93.2* (Constant)	Ultrasound	1 to 5	Single-row	40 of 50	50 of 52*
Flury[12] (2016)	Leukocyte-poor, platelet-rich plasma	120	24	82.1 (Constant)	82.7 (Constant)	Ultrasound or MRI	>0	Double-row	43 of 54	43 of 49
Zhang[30] (2016)	Leukocyte-rich, platelet-rich plasma	60	12	80.3 (Constant)	81.5 (Constant)	MRI	>1	Double-row	21 of 30	26 of 30
Zumstein[28] (2016)	Leukocyte-rich, platelet-rich fibrin matrix	35	12	80 (Constant)	80 (Constant)	MRI	>0	Double-row	11 of 18	11 of 17
Jo[25] (2015)	Leukocyte-poor, platelet-rich plasma	74	12	70.9 (Constant)	74.7 (Constant)	MRI	1 to 5	Double-row	24 of 30	32 of 33*
Malavolta[34] (2014)	Leukocyte-rich, platelet-rich plasma	54	24	85.2 (Constant)	84.8 (Constant)	MRI	<3	Single-row	22 of 27	25 of 27

*Significant at $p < 0.05$.

by 3 of the meta-analyses demonstrated improved outcomes with activated (solid) platelet-rich plasma compared with non-activated (liquid) platelet-rich plasma and improved outcomes in small and/or medium tears[35]. Additionally, subgroup analysis by 3 of the meta-analyses revealed application of platelet-rich plasma at the bone-tendon interface instead of over the repair, and the use of double-row repair compared with the single-row repair yielded improved outcomes[35]. However, the results of the meta-analysis must be interpreted with caution because the individual formulations of the platelet-rich plasma are often not known, and therefore the results may not be generalizable.

Based on these findings, the routine use of platelet-rich plasma in arthroscopic rotator cuff repair cannot be recommended. However, if a practitioner wishes to use platelet-rich plasma, data from the meta-analyses suggest that activated (solid) platelet-rich plasma delivered at the bone-tendon interface in conjunction with the double-row repair technique should be used. Further research evaluating whether differing formulations of platelet-rich plasma, as well as additional postoperative injections, would be beneficial especially if assessed in clinical scenarios in which the literature best supports the use of platelet-rich plasma.

Stem Cell Therapy

Rotator cuff healing is often compromised because of the lack of a local reparative cell population. This has led to the development of cell-based biologic augmentation of rotator cuff repair, using undifferentiated multipotent mesenchymal stem cells[36,37]. Initially discovered in bone marrow, mesenchymal stem cells have been isolated from adipose tissue, skin, synovial fluid, umbilical cord blood, placenta, and amniotic fluid[38-40]. Mesenchymal stem cells originate as pericytes, which are also known as Rouget cells or mural cells, and closely encircle endothelial cells in capillaries and microvessels[41,42]. Mesenchymal stem cells can differentiate into bone, cartilage, tendon, muscle, and adipose tissues in vitro[43,44]. The dominant impact of mesenchymal stem cells in vivo has been found to be via paracrine mechanisms, releasing trophic and immunomodulatory growth factors and

chemokines[40,45-47]. Mesenchymal stem cells possess anti-apoptotic[40,48,49], antimicrobial[50-52], and anti-inflammatory properties[53-55], and mesenchymal stem cell signaling promotes cell proliferation of several cell types, including endothelial cells, osteoblast-like cells, and progenitor cells[56,57], and angiogenesis[58]. Although debate exists for the optimal tissue source of autologous mesenchymal stem cells[59], the most commonly used are mesenchymal stem cells from bone marrow aspiration and adipose (adipose-derived stem cell) tissue[37,60]. Bone marrow is typically aspirated from the anterior or posterior iliac crest and then is concentrated using centrifugation to create bone marrow aspirate concentrate, which contains mesenchymal stem cells and other progenitor cells[61]. An adipose-derived stem cell is prepared by obtaining adipose tissue through either a lipoaspiration technique or an arthroscopic harvest[62-65] before mechanical fractionation and centrifugation[66]. In bone marrow concentrate, only 0.001% to 0.01% of the nucleated cells are mesenchymal stem cells[43,67], and 1% to 4% of the nucleated cells are mesenchymal stem cells in adipose-derived stem cell preparations[68]. Stem cell treatments can be administered via intraoperative or postoperative injection.

Although no randomized controlled trials examining the use of mesenchymal stem cells for rotator cuff repair have been published to date, there are animal studies that support their potential use[69-71] as well as lower-level evidence clinical studies for bone marrow aspiration concentrate and adipose tissue, both of which are known to contain mesenchymal stem cells along with other progenitor cells[37,60,61]. Hernigou et al.[72] followed 90 patients in a case-controlled study for 10 years after rotator cuff repair. Forty-five patients with full-thickness tears of the supraspinatus measuring a mean diameter of 1.5 ± 0.5 cm to 2.5 ± 0.5 cm were treated arthroscopically using a single-row technique and augmented with autologous bone marrow aspirate concentrate from the iliac crest injected at the bone-tendon interface and also into the bone at the site of the footprint. These patients were compared with 45 patients matched for tear size, rupture location, shoulder dominance, age, and sex who received the same surgical technique alone without bone marrow aspirate concentrate augmentation. At the 6-month follow-up, 100% of the patients receiving bone marrow aspirate concentrate had healed tears compared with 67% in the control group. At the 10-year follow-up, 87% of the patients who received bone marrow aspirate concentrate had intact repairs on ultrasound and magnetic resonance imaging (MRI) compared with only 44% in the control group. The re-tear rate was inversely correlated with the concentration of mesenchymal stem cells delivered, with patients receiving fewer mesenchymal stem cells more frequently demonstrating loss of tendon integrity compared with those who received more mesenchymal stem cells. Furthermore, quantitative analyses have demonstrated that bone marrow aspiration from the iliac crest produces a higher mesenchymal stem cell yield compared with other sources, such as the proximal parts of the humerus and tibia, suggesting that a greater benefit could be realized using a bone marrow harvest with a higher mesenchymal stem cell yield[73].

Another method to introduce bone marrow-derived mesenchymal stem cells to the repair site is via the penetration of the subchondral plate via the use of a drill or awl, thereby creating communication between the bone marrow and rotator cuff footprint following repair. In a non-randomized trial, Jo et al.[74] enrolled 124 patients for arthroscopic repair of a full-thickness rotator cuff tear, using the double-row technique whenever possible, with 57 patients undergoing multiple channeling and 67 patients undergoing the repair without multiple channeling. The re-tear rate of the multiple channeling group (22.2%) was significantly lower ($p = 0.023$) than that of the control group (45.2%), although there was no significant difference in clinical outcomes between the 2 groups. Similarly, Taniguchi et al.[75] utilized a comparable technique of bone marrow stimulation, drilling 4 to 6 small osseous holes at the footprint during repair. One hundred and eleven consecutive patients with full-thickness rotator cuff tears were enrolled for arthroscopic primary repair; 67 repairs were performed with bone marrow stimulation and 44 repairs were performed without. Subgroup analysis revealed a significantly lower re-tear rate and significantly greater cuff integrity for large or massive (>3 cm) tears in the bone marrow stimulation-treated group compared with the control group (28.6% compared with 4.5%; $p = 0.025$). Local extravasation of bone-marrow-derived mesenchymal stem cells appears to be beneficial, even though patients with symptomatic rotator cuff tears have decreased mesenchymal stem cell counts (30% to 70% less) at the greater tuberosity of the proximal part of the humerus compared with those without rotator cuff injury[76].

In addition to bone marrow aspiration, adipose-derived stem cells may be a viable biologic augmentation in rotator cuff repair. Kim et al.[77] evaluated 35 patients who underwent an arthroscopic double-row suture bridge technique repair with an injection of adipose-derived mesenchymal stem cells loaded in fibrin glue and compared with 35 patients matched for sex, age, and lesion size who underwent the same procedure without the adipose-derived stem cell injection. MRI evaluation demonstrated improved structural outcomes, with a significantly lower re-tear rate ($p < 0.001$) in the adipose-derived stem cell injection group (14.3%) compared with the control group (28.5%). After a 28-month follow-up, conventional repair and adipose-derived stem cell-augmented repair improved Constant-Murley score (referred to throughout this article as the Constant score) and University of California at Los Angeles (UCLA) shoulder scores, but there was no significant difference between groups.

Augmentation of rotator cuff repair with stem cells has exhibited

promising results in most studies, and its potential impact appears to be greater than platelet-rich plasma treatment. However, even though well-designed Level-III studies have shown long-term improvement in the re-tear rate with the use of bone marrow aspiration[72], to our knowledge, there have been no randomized controlled trials performed that examine this. Furthermore, improvement in radiographic re-tear rates may not always translate into improved clinical outcome scores. Bone marrow stimulation at the proximal part of the humerus demonstrated a decreased re-tear rate[75] although mesenchymal stem cell sources of greater yield, such as the iliac crest, may produce superior results. Because of an overall relative paucity of clinical outcome data, stem cell augmentation cannot be universally or definitively recommended in all cases of rotator cuff repair. High-quality, randomized controlled trials will need to be performed before the routine use of stem cell augmentation can be endorsed.

Biologic Grafts

The repair of massive rotator cuff tears poses a challenge for patients and surgeons, as the mechanical and biologic environments are suboptimal. Biologic scaffolding has been developed to promote healing while providing enhanced initial mechanical support and protection of repair and allowing for stress transfer and tissue ingrowth. There are different types of matrices available: xenografts (from other species), allografts (from humans), and autografts (from the same patient). There are also 2 main surgical techniques to utilize the scaffolding. The interposition technique uses scaffolding to bridge rotator cuff tendon defects; however, it is unable to compensate for reduced biomechanical factors associated with retraction of the torn tendons such as suboptimal working length and fatty infiltration and is not approved by the U.S. Food and Drug Administration (FDA) for this use in the United States (off-label use). The augmentation (overlay) technique uses scaffolding to reinforce tendon repairs that have reduced structural properties.

There has been 1 Level-III study evaluating the use of interposition autograft using biceps tendon and 1 Level-III study evaluating fascia lata interposition autograft compared with a tensioned primary rotator cuff repair group. Mori et al.[78] demonstrated that the use of a bridging fascia lata autograft led to a significant decrease in the re-tear rate of the infraspinatus (8.3% compared with 41.7%; $p = 0.015$) and resulted in improved Constant and American Shoulder and Elbow Surgeons (ASES) scores in large (>3 cm) or massive rotator cuff tears with low-grade fatty degeneration (Goutallier grade 1 to 2)[79] compared with partial primary rotator cuff repair under tension. Subsequently, Mori et al.[80] compared fascia lata autografts in patients with high (grade 3 or 4) and low (grade 1 to 2) Goutallier fatty infiltration and showed significantly worse structural integrity as well as Constant and ASES scores in the higher Goutallier grade group. Cho et al.[81] showed complete healing in 58% (compared with 26% without biceps interposition; $p = 0.036$) of massive rotator cuff tears via MRI using a bridging biceps autograft repair; however, they were unable to demonstrate improvement in functional testing. High healing rates have also been shown in observational and case control series of allograft interposition reconstructions (70% to 90%) and xenograft interposition reconstructions (73% to 100%)[82-88] with general improvements in patients' clinical outcome score. Table IV summarizes the clinical and radiographic results of Level-IV case series involving the use of biologic patches utilized as an interposition graft[80,82-86,89-93].

The best results using graft augmentation for large or massive rotator cuff tears have been achieved using acellular human dermal allograft matrix. Barber et al. showed in a Level-II study that the augmentation of an acellular human dermal allograft matrix, for tears >3 cm, led to significantly more intact repairs (85% compared with 40%; $p < 0.01$) and improved ASES and Constant scores at a mean of 14.5 months compared with repair alone[94]. Conversely, Iannotti et al. were unable to show a difference in clinical outcomes in a Level-II study when >3-cm tears were reinforced using porcine small intestine submucosa (xenograft) augmentation compared with repair without augmentation[95]. Although there have been studies that have shown improvement in the re-tear rate and clinical outcomes with xenografts[89,96,97], there also have been reports of severe postoperative inflammatory reaction necessitating reoperation with debridement[98].

In a comprehensive systematic review of Level-II through IV studies examining clinical outcomes and re-tear rates using biologic grafts of all types in rotator cuff repair, Steinhaus et al.[99] reported similar improvements in range of motion, strength, and patient-reported outcomes between augmentation and interposition techniques. Xenografts showed less improvement in patient-reported outcomes and activities of daily living than other graft types. Re-tear rates of 44% were shown for xenografts and re-tear rates of 23% were shown for allografts[99].

The optimal usage of biologic grafts in rotator cuff repair is still being defined as there is a lack of multiple high-level studies evaluating their effect on clinical outcome scores and re-tear rates. With few exceptions[81], many studies have shown good clinical outcome and repair rates for allograft in which patient selection was not standardized and control groups were not utilized. As a group, xenografts have shown less improvement in patient-reported outcomes compared with allograft[87]. However, it is important to not combine the results of biologic graft studies together as the graft structural properties are not similar, and the results may also differ based the surgical application (interposition compared with augmentation). In addition, there are profound differences in tissue

TABLE IV Level-IV Case Series of Biologic Grafts in the Bridging Reconstruction of Irreparable Rotator Cuff Tears

Study	Graft Type	No. of Patients	Outcome Score *(points)*		Imaging Method	Tear Size	Arthroscopic Approach?	Intact Repairs *(%)*
			Preoperative	Postoperative				
Bond[82] (2008)	Allograft, graft jacket	16	53.8 (Constant)	84* (Constant)	MRI	Massive, irreparable	Yes	81
Gupta[83] (2012)	Allograft, graft jacket	24	66.6 (ASES)	88.7* (ASES)	Ultrasound	Massive, irreparable	No	74
Varvitsiotis[84] (2015)	Allograft, fascia lata	68	32.5 (Constant)	88.7 (Constant)	Ultrasound	Massive, irreparable	No	90
Jones[85] (2015)	Allograft, acellular dermal matrix	106	14.6 (UCLA)	28.8* (UCLA)	MRI	Massive, irreparable	Yes	74
Petri[90] (2016)	Allograft, acellular dermal matrix	12	64.5 (ASES)	86.0 (ASES)	MRI	Massive, irreparable	No	83
Badhe[89] (2008)	Xenograft, Zimmer patch	10	41.5 (Constant)	62.5* (Constant)	MRI and ultrasound	Massive, irreparable	No	80
Gupta[86] (2013)	Xenograft, Conexa	27	62.7 (ASES)	91.8* (ASES)	Ultrasound	Massive or 2 tendon	No	73
Scheibel[91] (2007)	Autograft, humerus periosteum	10	50.5 (Constant)	79.9 (Constant)	MRI	Full thickness	No	57
Rhee[92] (2008)	Autograft, biceps tendon	34	48.4 (Constant)	81.8* (Constant)	MRI	Massive, irreparable	No	64
Sano[93] (2010)	Autograft, biceps tendon	14	54.7 (Japanese Orthopaedic Association)	83.1 (Japanese Orthopaedic Association)	MRI	Massive, irreparable	No	93
Mori[80] (2015)	Autograft, fascia lata	45			MRI	Large to massive, >3 cm	Yes	47
Low-grade fatty infiltration	Autograft, fascia lata	26	38.7 (Constant)	78.4* (Constant)	MRI	Large to massive, >3 cm	Yes	73
High grade fatty infiltration	Autograft, fascia lata	19	40.7 (Constant)	63.9* (Constant)	MRI	Large to massive, >3 cm	Yes	11

*Significant when preoperative scores were compared with postoperative scores.

processing, sterilization, and potential immunogenicity among the various commercially available grafts that further confound interpretation of published clinical results. Future investigations should focus on high-level clinical trials of biologic grafts used in rotator cuff repairs in muscles, preferably with lower grades of Goutallier fatty infiltration.

Conclusions

Biologic augmentation in rotator cuff repair has been an area of increased interest over the past couple of decades in the hopes of enhancing the healing environment and durability of rotator cuff repair over time. Summarizing recommendations for clinical care (Table V) for the variety of biologic treatments currently available is limited by the heterogeneity of the formulations in terms of cell and tissue type, processing, sterilization, processing, delivery

TABLE V Recommendations for Care Based on Grades of Recommendation for Summaries or Reviews of Orthopaedic Surgical Studies

Treatment	Grade*
Universal use of platelet-rich plasma in every arthroscopic rotator cuff repair cannot be recommended on the basis of numerous Level-I studies.	A
The application of bone marrow aspirate along with single-row rotator cuff repair has been shown to decrease re-tear rates in the short term and long term in 1 case-control study.	B
Because of a paucity of clinical data, stem cell augmentation cannot be universally or definitively recommended in all cases of rotator cuff repair.	I
Acellular human dermal allograft matrix used to augment rotator cuff repair has been shown to decrease re-tear rates and improve clinical outcomes compared with repair alone.	B
Xenograft augmentation has been shown to have no effect on re-tear rates or clinical outcomes compared with control.	B

*Grade A: Good evidence (Level-I studies with consistent findings) for or against recommending intervention. Grade B: Fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention. Grade C: Conflicting or poor-quality evidence (Level-IV or V studies) not allowing a recommendation for or against intervention. Grade I: There is insufficient evidence to make a recommendation.

method, concentration of active agent, timing, and surgical technique during rotator cuff repair. Additional trials focusing on clinical outcomes should be performed that optimize tear characteristics, formulations, and applications of the biologic agent to help to determine the appropriate use of biologic augmentation in rotator cuff repair.

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