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Scientific developments and clinical applications utilizing biologic augmentation for rotator cuff repair: a systematic review

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SCIENTIFIC DEVELOPMENTS AND CLINICAL APPLICATIONS UTILIZING BIOLOGIC AUGMENTATION FOR ROTATOR CUFF REPAIR: A SYSTEMATIC REVIEW

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ABSTRACT

Background: The radiologic failure rate of arthroscopic rotator cuff repair varies between 11-94%. Despite the advances that have been made in the surgical technique, recurrent tear continues to pose a significant problem. Biologic augmentation with 1. Implanted scaffolds, 2. Biologic injections, and 3. Marrow stimulation have the potential to strengthen the suture-tendon junction and enhance the cellular environment within the joint to encourage healing of native tissue, thereby improving surgical repair outcomes.

Purpose: This systematic review will discuss three major categories of RCR augmentation in both preclinical and clinical settings.

Study Design: Systematic Review

Methods: Aa systematic review of the past 10 years of the PubMed database was completed using PRISMA guidelines. Studies were classified as preclinical or clinical, and then further subdivided by augmentation category: grafts/scaffolds, injectable biologics, and marrow induction. This resulted in 87 studies as follows: 42 graft/scaffolds- 12 clinical and 30 preclinical; 37 injectable biologics-7 clinical and 30 preclinical; and 8 marrow induction- 6 clinical and 2 preclinical.

Results: Preclinically, a scaffold enhanced the healing potential of a torn, native rotator cuff tendon, with most included studies being biologically-based augmentation techniques demonstrating benefit in load-to-failure, stiffness, and strength. No study indicated a detriment to the repaired rotator cuff. Data on graft-based constructs were limited, with two autograft studies displaying inconsistent results. The majority of included preclinical studies exhibited improved enthesis maturation score and superior histological organization. All twelve clinical studies utilized scaffolds and indicated limited adverse implant-related complications with similar or improved patient-reported outcome measures compared to control repairs. Clinically, grafts/scaffolds and marrow stimulation have demonstrated positive outcomes when augmenting rotator cuff repairs. Preclinical injectables included a wide range of substances such as transforming growth factor β3, erythropoietin, bone marrow & adipose derived mesenchymal stem cells and platelet rich plasma with ozone. Preclinically, the most used injectable was stem cell-based biologics; it was found to have improved load-to-failure and histological findings. The most common findings for preclinical injectables were increased load-to-failure (51.7%) and improved collagen histological quality (31%). Clinically, platelet rich plasma and adipose-derived mesenchymal stem cells have shown potential to enhance rotator cuff repair results with further optimization of delivery methods, such as incorporation within a fibrin matrix. Lastly, marrow stimulation is promising both histologically and mechanically, demonstrating thicker collagen bundles and greater mean load-to-failure in rabbit models. Clinically, marrow stimulation has demonstrated variable but overall positive outcomes when augmenting rotator cuff repairs. Marrow stimulation techniques have demonstrated significant post-operative reduction in pain and improvement in function. Deep marrow venting significantly reduces retear rate relative to stand-alone single-row or double-row repair with limited adverse effects. Vented anchors demonstrated improved ossification and bone density at the anchor site, but no clinically significant difference in outcomes or retear rate.

Conclusion: Recent advances in 1. Grafts and scaffolds, 2. Injectable biologics, and 3. Marrow stimulation have helped promote the cellular environment within the joint and demonstrate favorable results in both preclinical and clinical settings. Clinically, grafts and scaffolds have proven to be safe and effective in treating rotator cuff tears, offering a promising means to improve rotator cuff repair load-to-failure, stiffness, and strength. Incorporation of injectable biologics into RCRs has shown the potential for enhanced healing of the biologic intra/extra cellular environment. There are a wide range of biologic compositions, preparation processes, and delivery methods in use. Though additional clinical data is needed, pre-clinical and clinical studies suggest injectable biologics may improve tendon quality and patient outcomes. Finally, marrow stimulation has demonstrated very high healing rates in primary rotator cuff repair and is promising in this setting. Current evidence demonstrates that microfracture and marrow-venting techniques may have a positive impact on healing and retear rate, while vented anchors have muted impact relative to non-vented anchors. Though available evidence is limited and more research is needed, findings to date suggest marrow stimulation techniques may be an inexpensive, simple technique to consider in qualifying patients to prevent rotator cuff retears.

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LIST OF ABBREVIATIONS

ASES	American Shoulder and Elbow Surgeons
bFGF	basic fibroblast growth factor
BMAC	bone marrow aspiration concentrate
ECM	extracellular matrix
IGF-1	insulin-like growth factor 1
MSCs	mesenchymal stem cells
PCL	polycaprolactone
PDGF	platelet-derived growth factor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMs	patient-reported outcome measures
PRP	platelet rich plasma
RCR	rotator cuff repair
RCT	rotator cuff tear
SF-36	36-Item Short Form Health Survey
SST	Constant-Murley Simple Shoulder Test
TGF-β	transforming growth factor beta
VEGF	vascular endothelial growth factor
WORC	Western Ontario Rotator Cuff Index

CHAPTER 1

The rotator cuff is a group of four muscles (supraspinatus, infraspinatus, teres minor, and subscapularis) that allow for a large range of motion by aiding in abduction, medial rotation, and lateral rotation of the shoulder while also providing stability to the glenohumeral joint (Drake et al., 2017). The glenohumeral joint is a ball and socket joint that consists of the humeral head and the glenoid fossa (Drake et al., 2017). The rotator cuff muscles help to stabilize this joint by compressing the humeral head against the glenoid to prevent sliding (Drake et al., 2017). These muscles attach to the anterior and posterior scapular surface and the greater and lesser tubercles of the proximal humerus and are especially prone to injury in overhead movements (Drake et al., 2017). Rotator cuff tears are the most common injury of the glenohumeral joint and have only increased in prevalence as our population continues to age (May & Garmel, 2021). There are multifactorial causes that lead to rotator cuff tears including degeneration, impingement, and tension overload due to injury (Maruvada et al., 2021). Often times, rotator cuff tears initially are partial tears of the supraspinatus tendon that over time progress into full-thickness tears when left untreated (Maruvada et al., 2021). Once a rotator cuff tear has developed into a full-thickness tear, surgical repair of the rotator cuff is often required. However, partial-thickness small rotator cuff tears have the greatest healing potential and therefore nonoperative treatments such as anti-inflammatory drugs, physical therapy and rehabilitation exist to a facilitate the natural healing process. Torn tendons undergo the typical wound healing process which includes inflammation, tissue repair, and tissue remodeling (Zumstein et al., 2017). During the inflammatory phase, the injured tissue releases multiple cytokines to attract inflammatory cells (Zumstein et al., 2017). The attracted inflammatory cells release interleukin1-β and tumor necrosis factor α which triggers the inflammatory cascade to begin (Zumstein et al., 2017). Apoptosis of the tenocytes ensues to clear cellular debris in preparation for tissue remodeling (Zumstein et al., 2017). Muscle fibers degenerate in the process. At the same time, multiple factors in the transforming growth factor beta family are released to assist in regulating the gene expression to achieve homeostasis (Zumstein et al., 2017). After this inflammatory phase is complete, macrophages and fibroblasts are used for tissue remodeling (Zumstein et al., 2017). Unfortunately, these monocytes increase scar tissue formation during the tissue remodeling phase of the healing process which subsequently has a negative impact on the biomechanical properties of the shoulder (Zumstein et al., 2017). The newly formed scar tissue is composed of greater amounts of collagen type I rather than collagen type III (Thangarajah et al., 2015). These structural changes are irreversible and are often the targets for novel treatments attempting to improve rotator cuff healing rates (Thangarajah et al., 2015). In rotator cuffs, as the tear size increases, fibroblast population decreases (Longo et al., 2011). Smaller tears have higher volumes of fibroblasts that are proliferating and actively involved in the reparative process by creating new extracellular matrix and collagen structures to begin to rebuild the tendon and restore tissue integrity (Longo et al., 2011). Similarly, there is also a reduction in inflammatory cell infiltrate and blood vessels in larger rotator cuff tears (Longo et al., 2011). Therefore, small tears are able to recover without surgery due to increased fibroblast cellularity, increased inflammatory response, and higher rates of vascularization all of which contribute to the healing potential of these tendons (Matthews et al., 2006).

Rotator cuff repair is a common orthopedic procedure that has well-documented clinical efficacy in alleviating pain and improving shoulder function in patients with rotator cuff tears. The number of rotator cuff repairs has risen, with one study showing a 188% increase in total rotator cuff repairs from 2007 to 2015 (Day et al., 2019). Despite the considerable research on rotator cuff repair and the advances that have been made in the surgical technique; rotator cuff re-tear continues to pose a large problem for both surgeons and patients alike (Chalmers & Tashjian, 2020). While the occurrence of radiographic re-tear is as low as 11% at two-year follow up (Lafosse et al., 2008), re-tears of repairs for large to massive tears occur more frequently. One study demonstrated up to 94% mechanical failure in large-massive rotator cuff tears (Galatz et al., 2004). Additionally, multiple imaging studies show that most rotator cuff re-tears occur within 3-4 months following initial repair (Iannotti et al., 2013; Miller et al., 2011). These early postoperative failures suggest that tendon healing may be slower than anticipated, especially given reported results of a failed healing response and decreased vascularity that is associated with increased tear size (Y.-S. Kim et al., 2017; Matthews et al., 2006). Consequences of failed RCR include altered glenohumeral joint kinematics resulting in superior humeral translation, articular wear, and ultimately cuff tear arthropathy.

Authors typically cite inadequate mechanical strength and lack of biological healing as the primary modes of rotator cuff failure. Recent advances in suture materials and anchors have led to improved mechanical strength. Furthermore, innovative surgical techniques such as the double-row transosseous equivalent repair result in lower re-tear rates on MRI (Tudisco et al., 2013). Enhancements in repair techniques have improved time zero biomechanical properties, meaning biomechanical properties on the day of surgery, not considering their performance after they have been in situ for a period of time. However, biologic healing remains a significant challenge as depreciating rotator cuff integrity and tendon tear recurrence is associated with clinical deterioration in the long-term period (H. M. Kim et al., 2014; Vastamäki et al., 2013). The weak link in a rotator cuff repair construct is at the suture-tendon interface, which results in suture pull-through (Ponce et al., 2013). This suture pull-out is a consequence of poor tissue quality and may result in tear progression. Biologic augmentation has the potential to play a role in strengthening this tenuous junction between the suture and the tendon, thereby improving surgical repair outcomes. Exciting recent developments have been made in the field of biological augmentation of RCR in both the preclinical and clinical settings (McCormack et al., 2014).

The past decade has yielded many biologic strategies aiming to increase rotator cuff repair healing rates including overlay grafts and scaffolds, platelet rich plasma injections, bone marrow aspiration concentrate, microfracture, osteoporosis medications, and nandrolone administration. Early data has demonstrated promising results in decreasing re-tear rates and preventing progression to massive rotator cuff tears (Chahla et al., 2017). However, more extensive research in the laboratory and/or clinical setting is necessary for clinical translation. Overall, these advances can be divided in 3 major categories: 1. grafts/scaffolds (excluding superior capsule reconstruction), 2. injectable biologic growth factors/cells, and 3. autologous marrow induction.

Graft tissue is meant to supplement repaired native rotator cuff tissue, while scaffolds provide a structural footprint for biologic cells to attach on which the repaired rotator cuff undergoes healing via promoted tendon vascularization and growth. Scaffolds provide stability in the healing process by acting as a bridge between tendon and bone (Thangarajah et al., 2015). Scaffolds are typical made of an acellular extracellular matrix which helps with cellular growth and collagen deposition which provide stabilization until the tissue is strong enough to relay the muscle load onto the humeral head (Thangarajah et al., 2015). Biologic augmentation using grafts and scaffolds has demonstrated promising results in decreasing retear rates and preventing progression to massive rotator cuff tears (McCormack et al., 2014). Advancements in scaffold and overlay graft augmentation have been especially encouraging due to its ability to induce native tissue regeneration and to improve patient pain and functional outcomes.

Biologic injectables have been used in the treatment of a variety of orthopedic pathologies, including osteoarthritis, tendinopathies, degenerative disc disease, and fractures (Kubrova et al., 2020). Biologics stimulate release of growth-factor and anti-inflammatory cytokines in order to promote healing, improve tissue quality and alleviate symptoms. There is considerable variability in the types of biologics (e.g., growth factors, platelet rich plasma, and adipose-derived mesenchymal stem cells (MSCs)) and their preparations (e.g., hydrogels, saline suspensions, and electrospun matrises). The FDA has created expedited pathways to help support the exploration and utilization of regenerative products, including injectable biologics, however, they have also cautioned the use of regenerative medicine in orthopedic conditions due to potentially dangerous implications (FDA, 2020a, 2020b). Despite the wide variation in injectable preparation and injection technique, there has been improved understanding and implementation of the technologies. Early studies exploring the role of bone marrow augmentation demonstrate promise in reducing retear rates and avoiding progression to massive rotator cuff tears (Bilsel et al., 2017, 2017; Dierckman et al., 2018, 2021; Jo et al., 2013; Li et al., 2019; Osti et al., 2013; Pulatkan et al., 2020). However, additional evidence is required to elucidate indications for use and enable clinical translation.

Growth factors are a common biologic injection studied for rotator cuff repair due to their role in the enthesis healing. Multiple growth factors including TGF-beta, VEGF, IGF-1, PDGF, and bFGF regulate the inflammatory process, synthesis of the extracellular matrix, cell recruitment, proliferation, and differentiation (Longo et al., 2013). These growth factors can be found in platelet rich plasma which has led to many studies investigating the effectiveness of platelet rich plasma in generating normal collagen alignment in the torn tendon (Longo et al., 2013). Adipose-derived mesenchymal stem cells are stem cells collected from excess adipose tissue (Tsuji et al., 2014). These cells are capable of differentiating into various cell lineages offering promising regenerative properties (Tsuji et al., 2014). These adipose-derived stem cells are thought to be beneficial for tendon healing because they secrete many growth factors including bFGF, VEGF, IGF-1, and TGF-beta (Tsuji et al., 2014). Further, adipose-derived stem cells express growth factor receptors and thus are responsive to growth factors themselves

(Tsuji et al., 2014). Therefore, adipose-derived stem cells have the capability of stimulating recovery of tissue and mediating tissue regeneration.

Other injectables that have been researched include melatonin, hyaluronic acid, and recombinant human parathyroid hormone. One of the most common complaints of rotator cuff tear patients is sleep disturbance and increase pain at night (Longo et al., 2019). The reason for this is not entirely known, although it is thought that there is an increased cytokine production during this time (Longo et al., 2019). Melatonin is a mediator of nocturnal pain which is why its use has been investigated as an augmentation technique in rotator cuff repairs (Ha et al., 2014). Similarly, hyaluronic acid has been explored as an augmentation for rotator cuff repair to reduce pain and improve overall functionality of the shoulder joint. Hyaluronic acid is a polysaccharide that is secreted by synoviocytes and fibroblasts in the extracellular matrix and synovial fluid (Gigante et al., 2013). Hyaluronic acid helps to supply lubrication and shock absorption for the joint, may have anti-inflammatory properties and likely works to decrease pain by inhibiting the nociceptors (Gigante et al., 2013). Teriparatide is a recombinant human parathyroid hormone that works to enhance the tendon-to-bone interface due to its osteogenic and chondrogenic capabilities (Werner, 2019). The purpose of this study was to provide a focused, systematic review of these three major categories of rotator cuff repair augmentation in both preclinical and clinical settings.

CHAPTER 2

A systematic review was performed using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009). The search utilized the PubMed central database in December 2020. The search terms used were ((((microfracture) OR (vented anchors)) OR (platelet rich plasma)) OR (amnion)) OR (adipose tissue)) OR (bone marrow aspiration concentrate)) OR (nandrolone)) OR (augmentation)) OR (biologics)) OR (growth factors)) OR (gene therapy)) OR (stem cells)) OR (tissue engineering)) AND (((rotator cuff repair) OR (single-row repair)) OR (double-row repair)) with filters as follows: date range of January 1, 2010 to January 1, 2020; English language. Broad-based augmentation search terms were initially used in an effort to capture the highest yield of articles.

The initial search resulted in 1,007 titles, to which the following criteria were applied. Inclusion criteria were titles that specified rotator cuff repair and augmentation techniques in peer-reviewed journals. The exclusion criteria were review articles, systematic reviews, editorials, technique articles, those without reported patient outcomes or the appointed outcome surrogates, case reports, and articles focused on superior capsular reconstruction/not focused on rotator cuff repair. After application of these criteria, 246 titles remained for abstract review. The abstracts of the articles were then reviewed, excluding duplicates, and articles that were case series with <15 patients, review articles not previously eliminated, articles not related to rotator cuff repair, studies focused on augmentation that did not fall within the 3 categories described, studies with a minimum average follow-up of <24 months, or those without abstract for review. This process eliminated 57 more articles, leaving 189 for full text review. Full text inclusion criteria were studies with clearly reported healing rate, any patient reported outcome measure, and studies with clearly reported load-to-failure, load-to-gap, gap size, and stiffness for preclinical augmentation titles. For the graft/scaffold manuscripts, primary outcomes for pre-clinical studies included tissue remodeling and biomechanical data points while primary outcomes collected for clinical studies focused on repair healing rates and patient-reported outcomes. The included studies were further subdivided, with the categorization as graft or scaffold being based on augment of interest used in the methodology section of the manuscripts. If the utilized patch supported cellular repopulation and/or revascularization (i.e. stem cell sheets, tissue matrix, collagen scaffold, etc.), the study was labeled as ‘scaffold.’ If the augmentation primarily supplemented the strength of repaired rotator cuff tissue structurally with directly grafted tissue and has limited bioinductive activity, it was labeled as ‘graft’. Bioinductive implants are those that encourage the formation of new tendinous tissue over the surface of the tendon, creating a thicker tendon. In instances of uncertain categorization, designation was made secondary to author description in the publication. As shown in Table 1, the full text review resulted in inclusion of 95 studies as follows: 44 graft/scaffolds- 12 clinical and 32 preclinical; 39 injectable biologics-9 clinical and 30 preclinical; and 12 marrow induction- 6 clinical and 2 preclinical.

Table 1. Study Count of All Studies Included, Separated by Type (Preclinical, Clinical) and Implant Category (Grafts/Scaffolds, Injectable Biologics, Marrow Induction).

Review Study Count			
Implant	**Preclinical**	**Clinical**	**Total**
Grafts/Scaffolds	32	12	44
Injectable Biologics	30	9	39
Marrow Induction	2	6	12
Total	64	31	95

CHAPTER 3

Preclinical Study Results

A total of 64 preclinical studies were identified. 32 evaluated the effects of grafts/scaffolds, 30 evaluated injectable biologics, and 2 studied marrow stimulation. The type of graft varied greatly amongst studies, as did the preparation of injectable biologic. There were no serious complications reported from any category in the preclinical studies. The most common positive effect was an increased load to failure; though stiffness and histological grading scores were often higher in the intervention groups.

Preclinical Grafts/Scaffolds

Thirty-two preclinical studies were identified with various augments employed. The animal models were divided amongst rat (18/32, or 56.3%), rabbit (9/32, or 28.1%), dog (3/32, or 9.4%), and sheep (2/32, or 6.3%). Two of the preclinical studies focused on grafts (Table 2), while thirty preclinical studies focused on scaffolds (Table 3). Both of the preclinical graft studies used autografts, one with bursal tissue and the other with fascia lata. In a rat model using the bursal tissue autograft, Ficklscherer et al found improved elasticity (P = 0.003) and improved stiffness (P = 0.002), as well as increased collagen II production (P = 0.04) in the bursal patch (Ficklscherer et al., 2020). However, in a rabbit model using a fascia lata autograft, Kataoka et al found no difference in ultimate failure load or stiffness between the treatment and control groups at 8 weeks postoperatively, although it was higher and statistically significant in the augment group initially at 4 weeks (Kataoka et al., 2018).

The specific augments for the scaffold preclinical studies were more varied, with the most common scaffold being collagen-based (10/30, or 33.3%), followed by engineered biomaterials (9/30, or 30%). The most common positive effect of the preclinical scaffold studies was an increased load to failure; stiffness and histological grading scores, such as collagen density/orientation and tissue vascularity, were also often higher in the intervention groups. Kaizawa et al used a tendon-derived collagen gel scaffold in a rat model and found significantly higher load to failure, stiffness, and energy to failure ($P < 0.05$) (Kaizawa et al., 2019). These biomechanical enhancements were coupled with improved histological outcomes, including greater areas of new collagen formation (Kaizawa et al., 2019). Similarly in a rat model, Zhu et al found that overall collagen scaffold augmentation improved histologic scores at 12 weeks ($P = .032$) (Zhu et al., 2019). These particular experimental results demonstrated a control (suture-only) group developing a bone-tendon junction predominantly consisting of direct fibers inserting onto bone without the formation a fibrocartilage transition zone, versus the scaffold group observing early maturation of a transition zone in 2 out of 5 specimens (Zhu et al., 2019).

Of the second most common scaffold, engineered biomaterials, Kim et al demonstrated synthetic scaffolds promoting superior tendon-to-bone healing with promising results using a polycaprolactone (PCL) scaffold mimicking the nanotopographic structure of native tendon tissue (W. Kim et al., 2020). The nanotopographic structure of the rotator cuff tendon refers to the sub-micron texture observed in the tissue that has anisotropic directional structures that play a role in the tissue function. This PCL scaffold showed improvements in histological scores of cell morphology, collagen arrangement, and vascularity ($P < .05$), compared to suture-only control, in chronic tear models in rabbits (W. Kim et al., 2020). Other scaffolds studied preclinically include autologously derived tissues (Chen et al., 2020), allograft tendon-cartilage-bone composite (canine patellar tendon) (Wang et al., 2020), and two used xenografts (ovine forestomach (Street et al., 2015) and multilayer canine hindlimb tendon tissue) (Omi et al., 2016). Two other preclinical scaffold studies utilized demineralized bone matrix in a rat model; Thangarajah et al demonstrated no significant differences between groups for enthesis maturation score fiber arrangement, cellularity, and vascularity (Thangarajah et al., 2017, 2018).

Overall, 25/32 studies, all of which utilized scaffolds, demonstrated positive biomechanical effects in terms of higher ultimate load-to-failure, stiffness, and strength. Improved histologic features such as number of fibroblasts, amount of visible collagen, and decreased amount of inflammatory tissue were also common findings across studies. There were no serious complications reported from any category in the preclinical studies. Individual characteristics of each study are outlined in Table 2 and Table 3. The results from the preclinical studies show promise regarding healing rates, loads-to-failure, and histologic characteristics of rotator cuff repair in animal models.

Only five of the 32 studies demonstrated a negligible effect from addition of a graft and/or scaffold (Kataoka et al., 2018; Street et al., 2015; Taylor et al., 2020; Thangarajah et al., 2017, 2018). No studies showed a negative effect after graft or scaffold addition.

Table 2. Overview of Preclinical Graft Study Results

Graft Preclinical Results					
First Author	**Journal/ Year**	**Specific Augment**	**Animal Model**	**Effect ***	**Representative Findings**
Ficklscherer	JSES 2020	Autograft: Bursal Tissue	Rat	+	Improved elasticity (*P*<.005); increased collagen II production in bursal patch
Kataoka	J Orthop Surg Res 2018	Autograft: Fascia Lata	Rabbit	0	No difference in ultimate failure load or stiffness

**Effect symbols: + positive effect, 0 negligible effect*

Table 3. Overview of Preclinical Scaffold Study Results

Scaffold Preclinical Results					
First Author	**Journal/ Year**	**Specific Augment**	**Animal Model**	**Effect***	**Representative Findings**
Street	J Orthop Surg Res 2015	Ovine Forestomach Matrix Scaffold	Rat	0	No difference in maximum load, elasticity, stiffness, or histologic characteristics
Omi	JSES 2016	Multilayer Xenograft (Canine Hind-Limb) + Biologics	Rat	+	Load to failure and stiffness significantly higher; histologically, improved tendon to bone healing
Wang	OJSM 2020	Tendon-Cartilage-Bone Composite (Canine Patellar)	Dog	+	Higher failure load and mean load to create 3mm gap
Huegel	J Orthop Surg Res 2017	Nanofibrous Scaffold + Autologous Tendon Derived Cells	Rat	+	Significantly increased stiffness and modulus; increased maximum stress; increased cellularity grade, cell delivery
Thangarajah	JSES 2017	Demineralized Bone Matrix (Collagen Scaffold + Growth Factors)	Rat	0	No significant differences between groups for enthesis maturation score, fiber structure and arrangement, vascularity, and cellularity

Thangarajah	AJSM 2018	Demineralized Cortical Bone Matrix Scaffold + MSCs	Rat	0	No significant increase in BMD by the addition of MSCs; more mature enthesis
Kim	Orthopedics 2019	Biomaterials: Alginate Sheet	Rat	+	Significantly higher ultimate load (*P*=.023) and ultimate stress (*P*=.02) and better total histological score (*P*=.02)
Yoon Arvinius	AJSM 2018 Injury 2020	Alginate Scaffold + Biologics	Rabbit; Rat	+	Statistically higher histologic score compared to other groups (*P*=0.001), and higher ultimate failure load Higher maximum load & elasticity
Kim	ACS Omega 2020	Nanotopographic Scaffold (Polycaprolactone)	Rabbit	+	Superior tendon-to-bone healing patterns and histological patterns in acute and chronic tear models
Rak Tarfder	AJSM 2020 Biofabrication 2019	Bioprinted Scaffold (Polycaprolactone) + Biologics	Rabbit; Rat	+	Superior histologic scores and motion analysis Maximum tensile load and tensile stiffness were significantly higher (p<.01); more CD146+ tendon progenitor/stem cells
Taylor	J Orthop Res 2020	Bilayer Delivery System (Polycaprolactone Nanofibrous Scaffold)	Rat	0	No difference between treatment groups biomechanically or histologically
Huang	JSES 2020	Hydrogel Scaffold + Microfracture + Biologics	Rabbit	+	Superior stiffness, load to failure, and tendon maturation score
Easley Su	JSES 2020 Int J Nanomedicine 2019	Biomaterials: PLGA Scaffold	Sheep; Rabbit	+	Vented anchors with PLGA scaffold have increased bone formation at tendon-bone interface Significantly greater BMD and bone volume/total volume and increased load to failure and stress to failure in GO-PLGA

Melamed	Am J Orthop (Belle Mead NJ) 2015	Chitosan Gel Scaffold	Rat	+	Number of fibroblasts and amount of repair tissue increased with less inflammatory response (fewer monocytes)
Kaizawa Zhu	J Hand Surg Am 2019 JSES 2019	Collagen	Rat; Rat	+	Significantly higher load to failure, stiffness, and energy to failure; higher BMD; increased area of metachromasia Scaffold augmentation improved histologic scores at 12 weeks (*P*=.032) but no improved biomechanical scores
Qian Zheng	Med Sci Monit 2019 Acta Biomater 2017	Collagen/Knitted Silk	Rabbit	+	Increased chondrogenesis, regenerative tissue and increased COL1 expression Higher ultimate force and energy (*P*<.05), but no difference in stress, stiffness, or collagen content
Kovacevic Peterson Tornero-Esteban Learn	Clin Orthop Relat Res. 2015 JSES 2015 J Orthop Surg Res 2015 J Biomed Mater Res B Appl Biomater 2019	Collagen Scaffold + Biologics	Rat; Sheep; Rat; Rabbit	+	No difference in area of fibrocartilage formation or collagen birefringence Statistically significant increase in bone growth; higher percentage of tissue that is tissue-like (p=0.002) Higher ultimate load at 3 months Significant difference in stiffness between seeded scaffold compared to scaffold alone (*P*=.03)
You Yea	Mol Med Rep 2018 Acta Biomater 2020	Hydroxyapatite Scaffold + Biologics	Rat	+	Collagen organization superior; higher ultimate load Superior in GAG and type 2 collagen scores at cartilage phase, calcification at bone phase, amount of newly formed collagen, and ultimate failure

Chen	AJSM 2020	Autogenous Urine-Derived Stem Cell Sheet	Dog	+	Biomechanically and histologically superior to repair alone
Shin	AJSM 2020	Stem Cell Sheet	Rat	+	Statistically better in maximum load and stiffness, better histologic score
Liu	Biomaterials 2019	Tendon-Fibrocartilage-Bone Composite + MSCs	Dog	+	Greater ultimate failure load and ultimate stress; improved collagen fiber organization and new fibrocartilage formation

MSCs, mesenchymal stem cells; PLGA, poly(lactic-co-glycolic acid).
**Effect symbols: +, positive effect; 0, negligible effect.*

Preclinical Injectable Biologics

Thirty studies were identified in total. Seventeen (56.7%) of the preclinical studies related to injectable biologics were performed in a rat model, eleven were conducted in rabbits (36.7%), two in mice (6.7%). Notably, no injectable was found to have a negative effect on outcomes in the preclinical setting.

Growth factors were the most common group of injectables investigated in the preclinical setting. All growth factors, except erythropoietin, were delivered in a gel/scaffold. There was a significant increase of load to failure in all growth factors when compared to the control, except transforming growth factor beta 3 (TGF- β3) combined with adipose derived stem cells and erythropoietin (Rothrauff et al., 2019). Interestingly, TFG- β3 alone improved load-to-failure similar to native tissue structure (Reifenrath et al., 2020). Another growth factor investigated that has had positive results is granulocyte colony stimulating factor (Buchmann et al., 2015). This is notable as high leukocytes counts in biologic injectables have previously shown worse outcomes (J.-H. Kim et al., 2021).

Bone marrow and adipose stem cells demonstrated both histological and mechanical benefits, including greater load-to-failure and reduced fatty infiltration. Common methods of delivery include gel and saline suspensions. Bone marrow stromal cells (BMSC) isolated from bone marrow aspirate demonstrated positive effects within the first 4 weeks, such as early increased load-to-failure and improved histological findings, when delivered within a gel. However, this short-term improvement was accompanied by increased stiffness of the graft, and there was no difference between experimental groups after 4 weeks, demonstrating the crucial role of method-selection in BMSC collection in yielding optimal results (Yonemitsu et al., 2019). Although BMSCs from bone marrow aspiration demonstrate a short term benefit (i.e. within the first 2 weeks following surgery) through improved fibrocartilage, isolating BMSCs from bone marrow aspirates may not be the most advantageous method of rotator cuff augmentation secondary to their mixed results. Overall, stem cell-based biologics were both the most commonly used and demonstrated the most promising results, such as increasing load-to-failure and reducing fatty infiltration.

A wide range of other injectables have been investigated, including melatonin, hyaluronic acid, and recombinant human parathyroid hormone. Gurger et al demonstrated platelet rich plasma (PRP) augmentation can be supplemented with gaseous ozone to improve both biomechanical and histopathological findings in a rat RCR model. The combination of PRP and ozone gas was shown to be a more effective intervention than either PRP or ozone alone (Gurger et al., 2021). Yea et al determined that RCR augmentation with human umbilical stem cells improved functional outcomes (e.g., walking distance, walking speed) in rabbits. Of note, this was the only preclinical study that investigated functional outcomes in an animal model (Kwon et al., 2018).

Increased load-to-failure was the most common biomechanical improvement, with 59.4% of preclinical injectables demonstrating increased load-to-failure. This improvement was not limited to a specific subset of substances. A variety of histological findings were also explored, with improved collagen quality and/or quantity demonstrated in 37.5% of the studies. Notably, none of the BMSCs provided lasting collagenous improvements. Five substances (botulinum toxin A, recombinant human parathyroid hormone, TGF-β3 + adipose-derived stem cells and BMSC from bone marrow aspiration) did not demonstrate any significant improvement in outcomes between the control and intervention group (Duchman et al., 2016; Gilotra et al., 2016; Rothrauff et al., 2019; Yonemitsu et al., 2019).

Table 4. Overview of Preclinical Injectable Biologics Study Results

Biologics Preclinical Studies					
First Author	**Journal/ Year**	**Specific Augment**	**Animal Model**	**Effect***	**Representative Findings**
Rothrauff	JSES 2019	TGF-β3 + Adipose Derived stem cells	Rat	0	No difference in load or stiffness compared to controls
Kaizawa	Hand Surg Am 2019	Stem cell-seeded human tendon-derived hydrogel	Rat	+	Significantly higher load to failure and higher stiffness
Reifenrath	JSES 2019	TGF-β3	Rat	-	Significantly higher load to failure and higher stiffness
Güleçyüz	SCRR 2018	Allogenic bone-marrow MSC	Rat	+	No significant increase in mean muscle mass; significantly less fattening (*P* <0.001)

Dyrna	AJSM 2018	Human bursal cells vs. bone marrow stromal cells	Mouse	+	Significantly higher number of cells infiltrating and more cells overall; increased healing tissue bridge ($P<.05$)
Lu	Chin Med 2018	Adipose stromal vascular fraction-containing stem cells	Rabbit	+	Increased maximum load, stiffness, and tendon-bone maturity scores ($p < .01$); higher expression level of collagen I, BMP-2, and quantified amount of BMP-2 ($P= 0.006$)[55] Maximum load, stiffness, and strength significantly greater t ($P < .01$ for all)
Wang	AJSM 2020	Adipose stem cell-derived exosomes	Rabbit	+	Significantly lower fatty infiltration ($P<.001$), higher stiffness, higher histological score, & more newly regenerated fibrocartilage at repair site
Song	Mater Chem 2019	Melatonin	Rat	+	Higher ultimate load, stress, and stiffness
Maillot	JSES 2018	Human subcutaneous adipose tissue	Rat	+	Better biomechanical properties ($P<.002$) 40% reduction in arthrofibrosis
Kwon	Stem Cells Int 2018	Human umbilical cord stem cell or polydeoxy-ribonucleotide injection	Rabbit	+	Newly regenerated collagen type 1 fibers; cell proliferation, angiogenesis, walking distance, fast walking time, and mean walking speed were greater
Wang	Arthroscopy 2018	Kartogenin	Mouse	+	Higher mean ultimate load of ($P=.04$) with superior collagen fiber organization ($P<.01$); Less % area of fibrocartilage ($P=.04$)
Kwon	AJSM 2018	Allogenic dermal fibroblasts	Rabbit	+	Mean load to failure significantly higher ($P= 0.011$); greater collagen fiber continuity

Liu	Clin Orthop Surg 2018	Bone marrow aspirate concentrate (BMAC)	Rabbit	+	Significantly higher ultimate load-to-failure, stiffness
Honda	AJSM 2017	Hyaluronic acid	Rabbit	+	No difference in load-to-failure; significantly more CD44 positive cells, more cartilaginous pellet produced, increased expression of type 2 collagen, SOX9, and aggrecan
Ozterme li	Orthop Surg 2019	Erythropoietin	Rat	+	Maximum load to failure significantly higher
Nuss	Ann Biomed Eng 2017	Poly-N-acetyl glucosamine	Rat	+	Significantly increased maximum load at 4 weeks; no histological differences
Tokunag a Yonemit su	JSES 2017 AJSM 2019	FGF-2-soaked gelatin hydrogels	Rat; Rabbit	+	Ultimate load to failure, stiffness, and ultimate stress to failure of the repair site were significantly higher; also showed significantly higher histological scores. Significantly higher ultimate load to failure and stress to failure
Novako va Degen	Orthop Res 2018 Arthroscopy 2016	Bone marrow stromal cells isolated from bone marrow aspiration	Sheep; Rat	0	Significantly less stiff than contralateral shoulders Early increase in failure load and stiffness (P = .002, <.0001) but by week 4 there were no significant differences. Increased fibrocartilage present at 2 weeks (p = .026)
Kim	JSES 2017	Acellular dermal matrix with stem cells	Rabbit	+	Mature tendons as time passed with cellular infiltration into the graft and evidence of neotendon formation
Arimura	AJSM 2017	TGF-β1	Rat	+	Significantly higher ultimate load to failure and higher collagen content
Ye	Acta Biomater 2020	Icariin	Rat	+	Significantly higher ultimate failure load, increased area of metachromasia, and

					significant increase in COL1 and COL2 production
Harada	Orthop Res 2017	Human rotator cuff cells	Rat	+	Significantly higher ultimate failure load[3]
Gilotra	BMC Musculoskelet Disord 2016	Botulinum toxin	Rat	0	At 4 weeks-increase ultimate load; more linear formation of collagen compared with the saline control group
Duchman	JSES 2016	Recombinant human parathyroid hormone on POD7	Rat	0	Significantly higher load to failure than controls early (*P* = .003); No difference in load to failure by 16 weeks
Cho	Orthop Res 2015	Tamoxifen	Mouse	0	Decreased atrophy and inflammation in the tamoxifen group but no significant difference in intramuscular adipocytes or lipid droplets
Buchmann	BMC Musckuloskelet Disord 2015	Granulocyte colony stimulating factor	Rat	+	Significant higher load to failure ratio (*P* = 0.020); significantly higher Collagen III content and I/III ratio

Preclinical Marrow Venting

Two studies evaluated marrow venting in rabbit models. Both found a positive effect in the intervention group as demonstrated by higher mean ultimate load-to-failure. Both also exhibited increased biology at the tear site with thicker collagen bundles on histologic examination (Arimura et al., 2017; Bilsel et al., 2017; Bryant et al., 2016). Marrow venting is a microfracture procedure where small holes are drilled through the bone until marrow elements enter the joint. Using a tuberosity microfracture model, Bilsel et al demonstrated that marrow venting resulted in a significantly greater mean ultimate load-to-failure at both 8 weeks (148.4 ± 31 N vs. 101.4 ± 26 N; P = .011) and 16 weeks (155 ± 30 N vs. 114.9 ± 25 N; P = .017) post-repair (Bilsel et al., 2017). Additionally, their model demonstrated no difference in linear stiffness or elongation at failure between the marrow stimulation and control groups (Bilsel et al., 2017). Similarly, Li et al demonstrated a significantly higher mean load-to-failure in a microfracture plus hyaluronic acid model at 12 weeks post-repair (100.5 ± 10.1 N vs. 68.0 ± 6.2 N; p = 0.012) (Li et al., 2019). Both also exhibited increased biology at the tear site with thicker collagen bundles on histologic examination (Bilsel et al., 2017; Li et al., 2019). In summary, preclinical data shows promising biomechanical and histological results when employing marrow stimulation in the setting of rotator cuff repair that merit further evaluation (Bilsel et al., 2017; Li et al., 2019).

Table 5. Features of Each Marrow Stimulation Preclinical Study Including Specific Augment, Animal Model, Effect, and Representative Findings.

Marrow Stimulation Preclinical Results					
First Author	**Journal/ Year**	**Specific Augment**	**Animal Model**	**Effect ***	**Representative Findings**
Bilsel	JSES 2017	Microfracture	Rabbit	+	Thicker collagen bundles; Higher mean ultimate failure load[4]
Li	J Orthop Translat 2019	Microfracture + Hyaluronic acid	Rabbit	+	Higher mean ultimate failure load; higher histological score[51]

* *Effect symbols: + positive effect*

In summary, the results from the preclinical studies in all categories (grafts and scaffolds, injectable biologics, and marrow stimulation) are promising regarding healing rates, loads-to-failure, and histologic characteristics of rotator cuff repair in animal models. These encouraging results combined with favorable safety profiles paved the way for clinical studies in human rotator cuff repair.

Clinical Study Results

A total of 27 clinical studies were identified across all three augmentation categories. Details of each individual study and the significant findings are displayed in Tables 6-8.

1. Clinical Grafts/Scaffolds

Combined with favorable safety profiles, these encouraging preclinical results paved the way for clinical studies in human rotator cuff repair. Graft tissue is meant to replace rotator cuff tissue, while scaffolds provide a structural footprint on which the native rotator cuff undergoes healing. Clinically, grafts and/or scaffolds have been targeted as a way to improve healing rates by supplementing the structural integrity of rotator cuff tissue (Ferguson et al., 2016). These grafts and scaffolds include xenografts such as porcine dermis and porcine small intestinal mucosa, human-derived allografts, extracellular matrix grafts, polyester patches, and collagen scaffolds. In the laboratory setting, as previously noted, this type of augmentation is successful in improving biomechanical and histologic outcomes. A representative image is demonstrated in Figure 1. All twelve of the included clinical studies focused on scaffold augmentation. Individual characteristics of the clinical studies are outlined in Table 6. The following discussion of clinical study results is divided by scaffold subtype.

Figure 1. Graphic representation of a repaired rotator cuff with anchors in the footprint incorporating native tissue and synthetic graft material, which overlies the repaired cuff. Attributed to Albert Mousad and Sarav Shah.

Table 6. Overview of Clinical Scaffold Study* Results

Scaffold Clinical Studies								
Implant Type	**First Author**	**Journal Year**	**Level of Evidence**	**Subjects (N)**	**Tear Size**	**Procedure**	**Post-Op Imaging**	**Significant Findings of Intervention Group**
porcine dermal (Conexa Reconstructive Matrix)	Castagna	Joints 2018	III	70	large	arthroscopic	MRI	Improved Constant score at 24mo (P=.036); subgroup analysis-those retorn on MRI + patch had higher functional scores (P=.0136)[49]
porcine dermal (Conexa Reconstructive Matrix)	Avanzi	JSES 2019	II	69	small & medium	arthroscopic	MRI	Lower retear rate (P<.001); higher tendon thickness and footprint coverage at two year follow-up[50]

porcine dermal (Conexa Reconstructive Matrix)	Lederman	JSES 2016	IV	50	large	arthroscopic	MRI	33.9% retear rate; 1 deep infection[51]
porcine dermal (Conexa Reconstructive Matrix)	Maillot	JSES 2018	II	32	large & massive	open	None	Improved functional scores in patch group versus debridement (P<.001), 1 deep infection and 4 arthrofibrosis in treatment group[52]
porcine small intestine (Restore Orthobiologic Implant)	Bryant	JSES 2016	I	60	medium & large	open	MRA	Relative risk of retear=0.81; 1 deep infection[53]
bovine collagen (REGENETEN)	Schlegel	JSES 2020	IV	33	partial-thickness	arthroscopic	MRI	95% high and 100% intermediate grade had tissue fill in with 1.8 and 1.2mm increased thickness, respectively[54]
bovine collagen (REGENETEN)	Thon	AJSM 2019	IV	23	large & massive	arthroscopic	MRI	96% healing rate; 91% clinical success rate[55]
human dermal matrix (ArthroFlex)	Gilot	Arthroscopy 2015	III	35	large & massive	arthroscopic	US	Lower retear rate; higher patient-reported outcome scores[56]
human dermal matrix	Hohn	JSES 2018	IV	23	>2cm retears	arthroscopic; revision	MRI/US	Symptomatic retear rate 17%; 13% underwent

(GraftJacket)								revision surgery[57]
extracellular matrix (Conexa/GraftJacket/Tisssue mend)	Sears	Orthopedics 2015	IV	24	NR; retears	open; revision	MRI/US	63% retear rate[58]
polyester patch (Pitch-Patch)	Smolen	JSES 2020	IV	50	large & massive	arthroscopic	CTA/MRA/US	14% retear rate[59]
3D-printed type I collagen	Cai	AJSM 2018	II	104	medium & large	arthroscopic	MRI	Lower retear rate[60]

MRA, magnetic resonance angiography; CTA, computed tomography angiography; MRI, magnetic resonance imaging; US, ultrasound; NR, not reported.
*All included studies were conducted with at least 2-year follow-up.

1a. Xenografts

Seven studies have reported on clinical outcomes following xenograft augmentation of rotator cuff repair. Four of these employed porcine dermal graft (Avanzi et al., 2019; Castagna et al., 2018; Lederman et al., 2016; Maillot et al., 2018), one porcine small intestinal mucosa (Bryant et al., 2016), and two with bovine collagen (Schlegel et al., 2021; Thon et al., 2019). In investigating porcine dermal matrix augmentation (Conexa Reconstructive Matrix; Tornier), a randomized control trial evaluated 69 patients at two-year follow-up, noting a significant difference in healing rates between the augmentation group (97.6%) versus the standard repair group (59.6%) ($P<.0001$) (Avanzi et al., 2019). Furthermore, the patients underwent a radiographic (MRI) evaluation of the rotator cuff at two years postoperatively, which showed greater tendon thickness (P=.012) larger footprint coverage (P=.0002) in the study group (Avanzi et al., 2019).

A separate study evaluating scaffold augmentation with the porcine dermal xenograft compared to a control repair group did not find a significant effect of the xenograft on healing rate, but it did find an improved Constant-Murley score at 24 month follow-up (P = .036) (Castagna et al., 2018). Maillot et al also found that this xenograft patch augmentation did not result in a significantly improved healing rate compared to a control repair group (Maillot et al., 2018). On the other hand, potential benefit was demonstrated in a prospective, multi-center study reported on 61 patients who underwent RCR of large (3-5 cm) tears with porcine dermal graft without a control group. The patients experienced statistically significant increases in American Shoulder and Elbow Surgeons (ASES), Constant-Murley Simple Shoulder Test (SST), and strength scores. On repeat MRI evaluation at 12 months, a retear of greater than 1c m was present in 19 (34%) patients. Four reoperations were also reported: three for revision repair and one for deep infection (Lederman et al., 2016).

Another porcine derivative, porcine small intestinal mucosa (Restore Orthobiologic Implant; DePuy), has also been evaluated as a potential xenograft augment. The small intestine submucosa (SIS) implant consists of ten tissue layers derived from submucosal tissue that supports a rapidly repopulating cellular population via an intricate architecture of a largely acellular connective tissue matrix of predominately collagen type I (90%) and water, combined with various growth factors and glycoproteins. One study found equivalent results between its standard repair groups and the intervention group noting no statistically significant difference in absolute risk of failure (P=.33), nor was there any difference for any of the PROMs (Western Ontario Rotator Cuff Index [WORC], ASES, SST, Constant-Murley, 36-Item Short Form Health Survey [SF-36]) at 1 or 2-year follow up (Bryant et al., 2016). Repair integrity was evaluated at one year via magnetic resonance arthrography and was found to be similar (Bryant et al., 2016).

Resorbable bovine collagen scaffold (REGENETEN; Smith & Nephew) has been used in small cohorts with promising results. This implant provides inducible collagen formation via a highly porous framework of highly purified collagen type I derived from bovine tendon designed to resorb entirely by 6 months. In patients with high-grade and intermediate-grade partial-thickness tears, 84% and 91% healing rates have been reported, respectively (Schlegel et al., 2021). In this study of 33 patients, all met minimal clinically important difference (MCID) for ASES and Constant scores, with an overall 80.6% satisfaction rate (Schlegel et al., 2021). Thon et al reported on patients who underwent both primary and revision RCR of large or massive tears augmented with a bioinductive bovine collagen patch, with a highly successful healing rate (22/23, 95%) and no adverse implant-related events (Thon et al., 2019). A remarkable finding in this study was the increase in tendon thickness on ultrasound evaluation during the study period.

In summary, the addition of a xenograft has mixed results regarding efficacy in augmenting RCR, demonstrating the importance of origin and immunogenicity treatment (Avanzi et al., 2019). There are promising results in small reports of bovine collagen xenografts with high healing rates and evidence of tendon thickening following implantation, suggesting increased healing potential at the repair site (Schlegel et al., 2021; Thon et al., 2019). Other clinical studies using porcine small intestinal mucosa found clinical outcome measures were similar between standard repair groups and xenograft-augmented groups. The studies that lacked a control group reported successful repairs as well as an increase in strength and PROMs from pre- to post-operatively. Importantly, the reported complication rate was low, which is promising for the safety profile of these xenograft tissues. Further randomized controlled trials are necessary to support the use of xenograft in rotator cuff repair augmentation.

1b. Acellular Dermal Allograft/Extracellular Matrix

Three studies specifically evaluated clinical results after implantation of acellular human dermal allograft (Gilot et al., 2015; Hohn et al., 2018; Sears et al., 2015), the largest of which comprised 35 patients (Gilot et al., 2015). This prospective comparative study found a significantly lower retear rate after allograft augmentation at two-year follow up: there were two retears (10.4%) in the allograft group compared to 4 retears (26.8%) in the control group ($P<.05$) (Gilot et al., 2015). Significantly better ASES scores ($P=.048$), WORC scores ($P=.044$), and improved (lessened) pain levels ($P=.013$) were also seen at 96-week follow up (Gilot et al., 2015). The authors concluded that acellular dermal extracellular matrix is a viable option during complicated cases in order to decrease the incidence of retear (Gilot et al., 2015).

Two smaller studies have investigated allograft supplementation of revision rotator cuff repair. Hohn et al reported a 17% retear rate (GraftJacket; Wright Medical);

however only 13 patients were available for radiographic follow-up (Hohn et al., 2018). Sears et al identified 62% retear rate at 4 year follow-up in the subset with imaging (Sears et al., 2015). This study also utilized a mixed group of dermal matrix augments, with Conexa (Tornier), GraftJacket (Wright Medical), and Tissuemend (Stryker), due to variable graft availability (Sears et al., 2015). Patient reported outcome measures status post revision repair with dermal allograft are variable, with favorable results in one study(Hohn et al., 2018), but 42% poor results in another (Sears et al., 2015), likely related to tissue status of the revision repair. Overall, the effect of acellular human dermal allograft augmentation is favorable and safe, though it may not be effective in revision repairs.

In summary, acellular dermal allograft augmentation of primary and revision rotator cuff repair is safe but may not improve repair results in the revision setting. While the extracellular matrix graft may provide structural integrity to a primary tear, a revision tear has already demonstrated decreased biology and may not benefit from graft augmentation. Similar to the xenograft results, the reported complication rate was low. These data demonstrate that the use of allograft tissue is low risk when augmenting rotator cuff repair.

1c. Polyester Patch

Only one study to date has evaluated the use of polyester patch for augmentation during repair of massive rotator cuff tears (Smolen et al., 2020). Constant-Murley and subjective shoulder values were significantly improved from preoperatively at all time points ($P<.0001$) (Smolen et al., 2020). Notably, the authors observed 7 (14%) complete recurrent tears, but these did not correlate with revision surgery; 6 of 8 revision surgeries were performed for arthrofibrosis with an intact cuff/patch (Smolen et al., 2020).

1d. Collagen Scaffold

One prospective, randomized control trial evaluated 104 patients comparing SutureBridge repairs to those augmented with synthetic 3D-printed type I collagen in medium to large rotator cuff tears (Cai et al., 2018). While the study group displayed higher outcomes scores at 6- and 12-month follow up, these effects were diminished by final, 24-month follow up (Cai et al., 2018). There was a lower retear rate in the augmentation group (13.7% versus 34% control, P=.02) (Cai et al., 2018). Interestingly, this study also employed histologic examination of rotator cuff tissue from three representative patients in either group. Biopsy specimens demonstrated much larger collagen fibrils formed at the tendon-bone interface in the augmentation group (P<.05) (Cai et al., 2018). Their histologic analysis allowed them to conclude that 3D collagen augmentation “could also promote new tendon-bone formation, thus exerting a prominent effect on tendon-bone healing” (Cai et al., 2018). In the studies evaluating collagen scaffolds, a positive effect was seen without adverse effects related to the implant. These studies display promise in the development of collagen augmentation of rotator cuff repairs, but further studies are needed.

2. Clinical Injectable Biologic Growth Factors/Cells

Biologic growth factors include a variety of substances such as TGF-beta, VEGF, IGF-1, among others. These molecules can be found intracellularly or extracellularly, such as in platelet rich plasma formations centrifuged from venous whole blood. In rotator cuff tears, PRP can be injected preoperatively in the office or intra-operatively to augment healing with autologous growth factors. In the laboratory setting, favorable effects have been found in rotator cuff repair augmented with various biologic growth factors both intracellularly and extracellularly, though few of these studies tested platelet rich plasma (Table 4). In the clinical setting, a very recent systematic review revealed that addition of PRP at the time of repair significantly reduced the retear rate in the long-term and provided enhanced function (Wang et al., 2020). Multivariate analysis demonstrated that use of leukocyte-poor plasma preparations and large/massive tear size were positively associated with decreased retear rate (Wang et al., 2020). Representative images of injectable biologics are seen in Figures 2 and 3 and individual characteristics of the clinical studies are outlined in Table 7.

Figure 2. Graphic representation of a repaired rotator cuff augmented with injectable biologic augmentation at the site of cuff repair. Attributed to Albert Mousad and Sarav Shah.

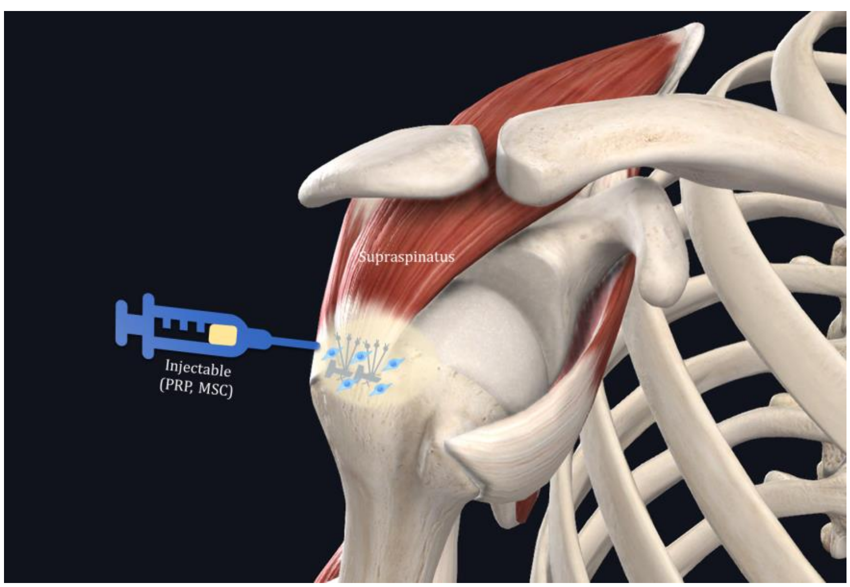

Figure 3. A: Completed rotator cuff repair of a left shoulder as viewed from the posterior portal in the beach chair position; **B:** Bone marrow aspirate concentrate injected via a spinal needle inserted through a portal site, overlying the repaired rotator cuff. Attributed to Albert Mousad and Sarav Shah.

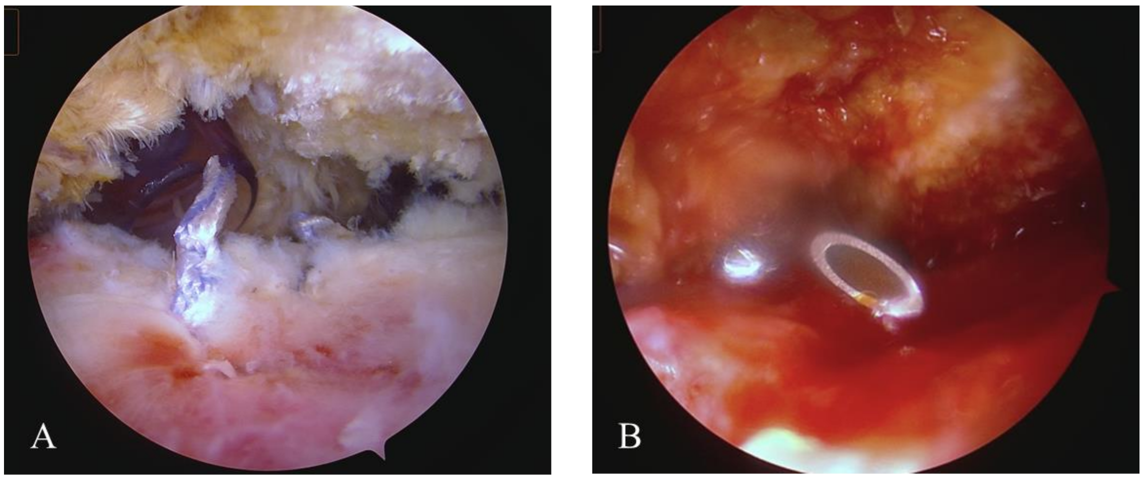

Table 7. Overview of Clinical Injectable Biologics Study Results

Biologics Clinical Studies								
Implant Type	**First Author**	**Journal Year**	**Level of Evidence**	**Subjects (N)**	**Tear Size**	**Procedure**	**Post-Op Imaging**	**Significant Findings of Intervention Group**
PRP	Malavolta	AJSM 2018	II	54	Small & medium	arthroscopic	MRI	No significant difference clinically or structurally
PRP	Walsh	JSES 2018	II	72	Small to large	arthroscopic	MRI	No significant difference clinically or structurally
PRP	Pandey	JSES 2016	I	102	Medium & large	arthroscopic	US	Lower retear rate in PRP group for large tears (P=.03); higher vascularity in PRP group at 3mo

Adipose-derived mesenchymal stem cells	Kim	AJSM 2017	III	70	Medium to massive	arthroscopic	MRI	Lower retear rate
PRP	Gwinner	Arch Orthop Trauma Surg 2016	III	36	<5cm	arthroscopic	MRI	No significant difference
PRP	Flury	AJSM 2016	I	103	NR; supraspinatus only	arthroscopic	MRI/US	No significant difference
PRP Gel	Dukan	Phys Sportsmed 2019	III	69	NR; supraspinatus only	arthroscopic	MRI	No significant difference
PRP	Randelli	Arthroscopy 2018	II	53	Massive	arthroscopic	MRI	Decrease in retear rates of small tears
PRP	Randelli	Arthroscopy 2022	II	38	Massive	arthroscopic	MRI	Significantly improved SANE scores

2a. Platelet-Rich Plasma (PRP)

Platelet-rich plasma as an adjunct in treatment of rotator cuff tears has been a major research focus over the past decade. Significant heterogeneity exists in the literature, with multiple trials failing to note any clinical outcomes or radiographic improvements over a control group with the use of PRP (Flury et al., 2016; Gwinner et al., 2016; Malavolta et al., 2018; Walsh et al., 2018). Other studies have pointed to an early positive effect at 3 months, but this benefit did not last until the two-year follow up

(Dukan et al., 2019). One report on over 100 patients noticed better pain scores in the PRP group at 1, 3, and 6 months postoperatively as well as improved Constant and UCLA scores in the mid-term. A statistically significant lower retear rate for large tears was present in the PRP group ($P=.014$), but not for medium tears ($P>.05$). Interestingly, this study also reported on vascularity as seen by ultrasound evaluation and noting early improvement in tendon vascularity and peribursal tissue that lasted until the 12-month follow up ($P=.003$) (Pandey et al., 2016).

In an effort to improve delivery of platelet-rich plasma to the repair site, one randomized control trial compared ultrasound-guided injection at 7 and 14 days postoperatively to controls who did not receive PRP. All patient reported outcome measures were statistically insignificant, including both subjective and range of motion subscales of the Constant score. MRI evaluation of retear rates did not differ between groups (Gwinner et al., 2016). The authors concluded that early results suggested higher strength and patient satisfaction, but no additional benefit to tendon integrity was seen following postoperative PRP administration. All of the recipients of the PRP injection were aware of their treatment status, however, so the reported patient satisfaction could have been biased due to the unblinded nature of the study. Recently, Liu et al compared administration of PRP intraoperatively to patients who received a 2 week PRP booster in addition to the intraoperative injection with a follow-up time of 1 year. It was found that in tears ≥ 2 cm there was a significantly improved retear rate (12.5% in overall PRP vs. 35.7% no PRP injection) (Liu et al., 2018). However, there were no differences in healing rates seen between the boosted and non-boosted group (Liu et al., 2018). Another group concentrated a PRP globule onto a fibrin matrix and shuttled the globule over a suture in an attempt to maintain concentrated PRP at the repair site over time. There was a statistically significant decrease in retears in the PRP group (30% vs 60% in control, P=.03) as seen on MRI evaluation. PROMs did not differ between groups with the exception of the Rowe score favoring the intervention group (Walsh et al., 2018).

Randelli et al have published both 2 and 10 year outcomes of a cohort of patients who had PRP augmentation of RCR (P. Randelli et al., 2011; P. S. Randelli et al., 2022). The PRP was collected using double centrifugation, was not activated and was delivered during the surgery. At 24 months, patients had significantly lower VAS scores compared to 3, 6 and 12 months post-operatively. There was initial clinical score benefits 3 months post-operation, but these benefits did not persist at the 2-year mark. Additionally, there was a decrease in retear rates of smaller tears (grades 1 and 2) compared to the control at the 2-year mark. At the 10-year mark, the PRP group had significantly improved single assessment numerical evaluation (SANE) scores compared to the control. However, there was no difference in retear rates or other clinical assessment outcomes at 10 years follow up.

Platelet-rich plasma may be a valuable means by which to deliver autologous growth factors to the site of rotator cuff repair, but the variable methods by which to obtain, concentrate, and deliver the PRP make comparisons between studies challenging. More recently, delivery postoperatively (to avoid washout by arthroscopic fluid) or in concentrated fibrin-matrix globules, have obtained better clinical and radiographic outcomes, respectively.

2b. Adipose-derived Mesenchymal Stem Cells

The only available data regarding implantation of mesenchymal stem cells is from Kim et al's 2017 study. This matched cohort study demonstrated improvement in range of motion as well as patient-reported outcomes in both groups without a statistically significant difference. On MRI evaluation, however, the retear rate was significantly lower in the intervention group (14.3%) than in the control group (28.5%) ($P<.001$) (Y. S. Kim et al., 2017). The authors concluded that the adipose-derived stem cell injection provided a favorable biologic environment about the repair site based on the lower retear rate. The harvest of autologous adipose-derived mesenchymal stem cells the day prior to surgery represents a potential disadvantage in that it requires additional patient and surgeon coordination.

3. Marrow Induction

Microfracture and marrow venting are methods of stimulating elution of marrow elements including mesenchymal stem cells, growth factors, and chemotactic cytokines via breaks in the proximal humeral cortex at the site of rotator cuff repair (Dierckman et al., 2018). Preclinical data is limited, but the few studies performed in the laboratory show promising results when employing marrow induction on rotator cuff repair both biomechanically and histologically (Bilsel et al., 2017; Li et al., 2019). A representative image is demonstrated in Figure 4 and individual characteristics of the clinical studies are outlined in Table 8.

Figure 4. Graphic representation of a rotator cuff repair augmented with bone marrow induction at the site of the humeral footprint. Attributed to Albert Mousad and Sarav Shah.

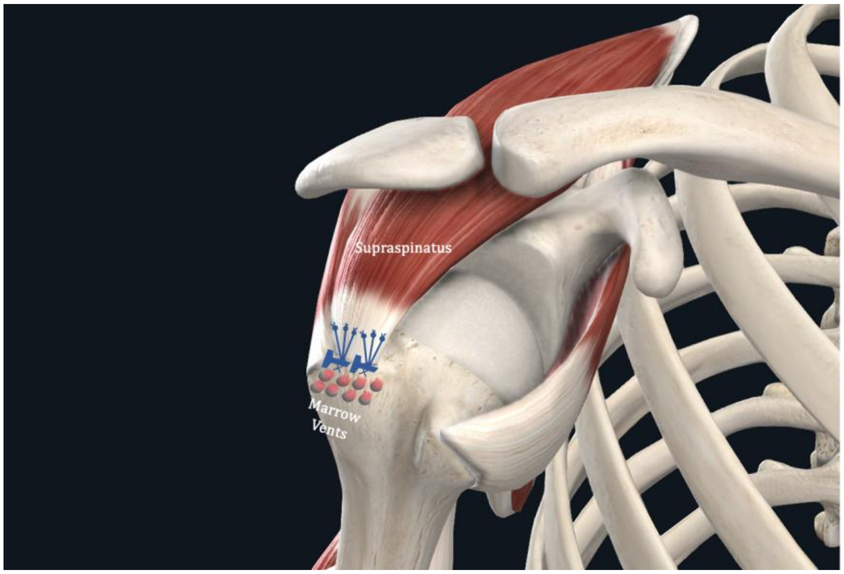

Table 8. Overview of Clinical Marrow Induction Study Results

Marrow Induction Clinical Studies								
Implant Type	**First Author**	**Journal Year**	**Level of Evidence**	**Subjects (N)**	**Tear Size**	**Procedure**	**Post-Op Imaging**	**Significant Findings of Intervention Group**
Multiple channeling	Jo	AJSM 2013	III	124	Small to massive	arthroscopic	MRI/ CTA	Lower retear rate in multiple channeling group
Marrow venting	Dierckman	Arthroscopy 2020	IV	91	Medium to large	arthroscopic	MRI	92% healing rate, 91% patient satisfaction
Marrow venting	Dierckman	KSSTA 2018	IV	52	Medium & large	arthroscopic	MRI	91% healing rate
Microfracture	Milano	Arthroscopy 2013	I	73	Medium & large	arthroscopic	MRI	higher healing rate in microfracture group compared to control only in

								subanalysis of patients with large two-tendon tears
Microfracture	Pulatkan	JSES 2020	III	123	large	arthroscopic	MRI	Lower retear rate
Microfracture	Osti	Int Orthop 2013	I	57	NR; full thickness	arthroscopic	MRI	No significant difference clinically or structurally

3a. Microfracture and Marrow Venting

Microfracture has been used as a form of marrow stimulation at the humeral footprint of rotator cuff repairs with variable effect (Bilsel et al., 2017; Dierckman et al., 2018, 2021; Osti et al., 2013; Pulatkan et al., 2020). A randomized control trial noted better pain and patient reported functional scores at 3 months following microfracture, but these were negligent at final follow-up (Osti et al., 2013). Healing rates were no different in this study. A separate level I study demonstrated high failure rates in both the microfracture group (34.3%) and the standard repair group (47.4%); however, a sub-analysis of large two-tendon tears showed a higher healing rate in the microfracture group (60% vs 12.5%, P<.04) (Milano et al., 2013). This study employed a small joint arthroscopic awl and described the perforations as 4 mm apart, 5 mm deep, and 1.5 mm wide. Since these publications, advances have been made aiming to deepen the channels for better delivery of marrow elements as well as to avoid compromising suture anchor fixation.

Deep marrow venting with the use of sharp, thin awls has been used to promote the release of marrow elements specifically, growth factors, at the site of rotator cuff repair. In a comparison of single-row repair with standard anchors plus marrow venting, versus both a single and double-row repair, the venting group had the lowest retear rate as demonstrated by MRI at 2-year follow up: 14% as compared to 33% in the single row group and 36% in the double row group (P=0.045) (Pulatkan et al., 2020). Other studies have demonstrated retear rates less than 10% following single-row repair with marrow venting (Dierckman et al., 2018, 2021).

In addition to lowering rates of retear, the delivery of mesenchymal stem cells to the repair footprint as a result of multiple channeling was confirmed with the use of flow cytometry (Jo et al., 2013). These cells were obtained at the time of surgery, then isolated and cultured, displaying positivity for CD73, CD90, and CD105. The authors found no significant clinical difference at two-year follow-up but anticipated that clinical outcomes would be maintained at longer term follow up due to the structural integrity provided by the mesenchymal stem cell delivery.

In summary, the six studies focused on marrow venting had no reported adverse effects related to the technique and high rates of rotator cuff healing. The three studies with a comparison group demonstrated favorable clinical outcomes in the microfracture groups despite a lack of statistical significance at final follow-up in two (Milano et al., 2013; Osti et al., 2013). Positive factors associated with MRI-confirmed rotator cuff healing included low levels of fatty infiltration (Dierckman et al., 2021; Milano et al., 2013). Negative factors for healing included higher patient age, duration of symptoms, and amount of tendon retraction; those these were reported in one study (Milano et al., 2013). The local presence of marrow elements including growth factors and cytokines combined with autologous mesenchymal stem cells likely provides a favorable milieu for tendon healing. An additional advantage to this technique is the ability for marrow elements to elute following the conclusion of the case without dilution by arthroscopic fluid. As compared to external injections such as PRP which are time-zero events, microfracture and marrow venting provide a continuous source of growth factors over time.

CHAPTER 4

Grafts/Scaffolds

Advances in repair techniques have improved time zero biomechanical properties, but biologic healing remains a significant challenge. Recent advances in graft and scaffold augmentation have helped promote the biologic milieu and demonstrate favorable results in both preclinical and clinical settings (Ferguson et al., 2016). Promising scaffolds include acellular dermal allografts/extracellular matrices, polyester patches, and bovine collagen scaffolds. These constructs have been targeted as a way to improve healing rates by supplementing the structural integrity and providing a scaffolding construct for biologic factor attachment for the repaired rotator cuff tissue (McCormack et al., 2014). There is evidence of clinical deterioration in the long-term period after tendon tear recurrence (H. M. Kim et al., 2014; Vastamäki et al., 2013). Contrary to widely held ideology that patients post-RCR have similar outcomes regardless of repair integrity, the presence of a retear has been shown to be negatively impact the clinical outcomes following rotator cuff repair (H. M. Kim et al., 2014). Furthermore, a re-torn or unhealed repair increases the risk of osteoarthritis, which is also associated with poorer clinical outcomes (Flurin et al., 2017).

Several factors can influence the postoperative prognosis of rotator cuff repair such as anteroposterior tear length, fatty infiltration of muscles, and reduced bone density and these indications of increased risk of failure may be opportunities to focus efforts of maximizing healing potential with targeted augmentation. The beneficial cost effectiveness of the RCR augmentation with graft/scaffold constructs in patients with anticipated risk for retear may provide a solution to optimize outcomes and improve the value of care of several patient populations.

One promising scaffold augment is the resorbable bioinductive bovine collagen implant (REGENETEN; Smith & Nephew), as it has shown preclinical and clinical results. Multiple studies show its safety profile (Thon et al., 2020). Basic science studies demonstrate collagen scaffolds lead to a higher percentage of repair tissue that is tendon-like and a higher load to failure (Arnoczky et al., 2017; Peterson et al., 2015). This correlates to clinical studies indicating significant improvements in patient-reported outcomes in the early post-operative period compared to control rotator cuff repair (Bushnell, Bishai, et al., 2021; McIntyre et al., 2019). Further benefits have already been demonstrated across various tear sizes, including maintenance of post-implantation tendon thickening and repaired strength of the augmented tissue in both partial-thickness and large-massive tears (Schlegel et al., 2021; Thon et al., 2019). Furthermore, although only 1 year follow-up, Bushnell et al, demonstrated beneficial results at 1 year after treatment with the bioinductive bovine collagen implant augmenting standard arthroscopic repair techniques including a favorable rate of retear relative to the literature and improvement in clinical function (Bushnell, Connor, et al., 2021). Ultimately, the evidence for the bovine collagen implant is clear that it helps improve PROMs significantly in the short-term with results declining in the long-term. Multiple studies, both preclinical and clinical, with large sample sizes across many different US centers with different orthopedic surgeons have demonstrated its short-term effects. However, these studies were not blinded which could have led to bias in the results. Therefore, this may be a great augmentation option for athletes or others in need of a more rapid recovery.

This signals a shift in the literature from earlier mixed results for xenograft patches, with recommendation against their use due to the presence of cellular material and/or DNA capable of inducing an immune reaction and significant inflammatory response (Derwin et al., 2006). One demonstration of this is the halting of a 2006 randomized control trial of porcine small intestine submucosa (Restore Orthobiologic Implant; DePuy) secondary to severe inflammatory reactions, inferior repair strength, and high retear rate(Iannotti et al., 2006; Sclamberg et al., 2004). Presently, improved processing techniques and lessons learned from past has directed the advancement of newer technologies with dramatically reduced implant-related adverse effects, as reviewed in this study.

Another promising scaffold is acellular human dermal allograft (ACD) (CuffMend; Arthrex). Despite a few clinical studies demonstrating variable results (Gilot et al., 2015; Hohn et al., 2018; Sears et al., 2015), acellular dermal matrix has an encouraging foundation of basic science research. Implementation in rat models demonstrated increased vascularity and cellular infiltration (Capito et al., 2012). In a canine model, decellularized human dermis showed significantly improved range of motion (ROM) and reduced pain as well as the most improved MRI pathology compared to control groups in a canine model (Smith et al., 2020). Further, one prospective comparative clinical study found a significantly lower retear rate and higher patient-reported outcome scores after ACD augmentation at two-year follow-up compared to the control non-augmented repairs (Gilot et al., 2015). Based on preclinical data and limited clinical evidence, the authors are cautiously optimistic in implementing these constructs in practice.

Injectable Biologics

A variety of injectable biologic augmentation in rotator cuff repair are being investigated such as TGF-β, adipose-derived stem cells, bone marrow aspirate, PRP and ozone. Approximately 80% of preclinical experiments demonstrated a positive biomechanical or histologic effect. Importantly, there was no overall negative effect seen by biologic injectable augmentation, demonstrating the considerable potential for clinical research translation.

Growth factors were the most common group of injectables investigated in the preclinical setting. All growth factors, except erythropoietin, were delivered in a gel/scaffold. This may have contributed to erythropoietin's inconclusive results. Utilization of a scaffold to stagger release of erythropoietin may be considered in the future to allow for a longer anabolic effect. Among growth factors investigated, nearly all showed a net positive effect. The most frequent positive effect was increased ultimate load-to-failure, a strong indicator of improved rotator cuff integrity. Transforming growth factors TGF-β1 and TGF-β3 currently show the most promise. Both share the same receptor complex and have been proven to play a crucial role in fibrosis and wound healing (Denaro et al., 2010). Reifenrath et al found that incorporation of TGF -β3 into an electrospun chitosan coated polycaprolactone fibre scaffold led to biomechanical maximum force values that were similar to the native tendon ($P \leq .01$). Surprisingly, Reifenrath et al found no improved histological findings with the biomechanical improvements (Güleçyüz et al., 2018). This is contrasted with Han et al's findings of improved histological findings with no biochemical improvements when delivered in tendon specific cross-linked gelatin. This highlights the importance of testing not only various biologic injectable compounds, but the vehicle active compound delivery as well. With further advances in biomaterials, such as utilization of nanocarriers to deliver TGF -β, expansion of delivery methods show promise in advancing preclinical development of growth factor delivery (Vander Ark et al., 2018).

Another recent advancement in the preclinical setting is the role of ozone augmentation of PRP injections in RCR elucidated by Gurger et al. Ozone therapy has been investigated in many acute and chronic tendinopathies but has yet to be investigated in RCR. It has been shown to increase the release of various platelet growth factors from PRP including PDGF, TGF- β1, and IL-8 (Gilotra et al., 2016). Gurger et al found that the combination of PRP and ozone lead to histopathology that resembled a healthy rabbit additionally, it resulted in the highest biomechanical findings. With increasing usage of PRP in the preclinical setting, it would seem judicious to further investigate the role of ozone in improving RCR outcomes. Ozone has been used for many musculoskeletal diseases due to its highly reactive nature, it can dissolve into tissue and enhance tendon-to-bone healing by stimulating a cascade of antioxidant formation leading to faster healing. Injection of ozone increases IL-8 which results in leukocyte recruitment and phagocytosis. Additionally, ozone has been shown to increase the presence of growth factors such as PDGF and TGF-beta resulting in greater tissue remodeling.

Both bone marrow and adipose derived MSCs have demonstrated an overall positive effect in the preclinical setting. Increased ultimate load-to-failure and improved histological findings, such as increased fibrocartilage quantity and quality, were found in both bone marrow and adipose derived MSCs. These results illustrate the potential for both bone and adipose derived MSC efficacy in clinical practice. Regarding translation to clinical practice, adipose derived MSCs are easier to harvest, and may provide fewer complications. Adipose-derived MSCs secrete growth factors such as TGF-beta, HGF, MMP, and VEGF that lead to the recruitment and proliferation of fibroblasts to the site of injury and promote angiogenesis. Of note, studies involving bone marrow MSCs specifically isolated from bone marrow aspiration demonstrated mixed/neutral results. Therefore, isolating BMSCs from bone marrow aspirates may not be the most advantageous method of BMSC preparation. Additionally, the FDA has made statements cautioning the use of adipose-derived MSCs for orthopedic treatment after little evidence has been published on their benefit.

Clinical exploration of injectables has been focused on PRP and adipose derived MSCs. While utilization of different delivery methods and timing may reduce the risk of arthroscopic washout of PRP, these innovative delivery techniques did not result in a statistically significant reduction in retear rates (Gwinner et al., 2016). As shown by Randelli et al, PRP administration utilizing double centrifugation and activation with calcium chloride may lead to permanent increases in SANE scores (P. Randelli et al., 2011; P. S. Randelli et al., 2022). Tear size may also play a role in deciding to augment repair with PRP, as they found that only grade 1 and 2 tears benefited from PRP injection at the 2-year mark (P. Randelli et al., 2011). One technique that has shown promise is delivery utilizing a fibrin matrix led to a significantly reduced retear rate (Walsh et al., 2018). Walsh et al prepared leukocyte poor PRP through double centrifugation followed by using calcium chloride for activation (Walsh et al., 2018). These three techniques of enhancing PRP preparation are not incorporated together in any other clinical trial found in this systematic review. Both the method of PRP preparation outlined above and growth factors within the PRP being released over a longer time period (approximately 30 days) likely contributed to the lower retear rate. Both improving PRP preparation and utilizing various modes of PRP delivery such as fibrin gels show potential in improving RCR biologic injectable augmentation and should be further explored as methods to enhance patient outcomes. Additional methods to improve the delivery methods of biologic injectables, including novel delivery matrixes, should be investigated in the clinical setting. Currently, there is a range of techniques and preparations used to prepare PRP (Dhurat & Sukesh, 2014). Future investigation and optimization of PRP collection and preparation in conjunction with improved delivery methods shows promise in improving RCR outcomes.

In clinical practice, adipose derived MSCs have been explored as an alternative to bone marrow derived MSCs due to easier harvestability and higher MSC proliferative capacity. Adipose derived MSCs are thought to upregulate tendon-related genes through immune modulation and differentiation (Lee et al., 2017). One clinical study by Kim et al explored adipose derived MSCs. 4.46 x 10^6 adipose derived MSCs were injected in 2 ml of fibrin glue to act as a scaffold. Results are promising with a 14.2% reduction in retear rates (Y. S. Kim et al., 2017). As with PRP, additional scaffolding techniques may be attempted in the future. Another area of potential investigation is utilization of Adipose derived MSCs without scaffolding, as adipose derived MSCs do not require scaffolding to exhibit anabolic effects on local tissues (Usuelli et al., 2017).Adipose derived MSCs have also been used in conjunction with PRP for other orthopedic pathologies such as osteoarthritis (Usuelli et al., 2017). Further work is warranted in determining optimal methods of delivery of adipose derived MSCs, as initial results show potential to improve patient outcomes.

There is promise in delivering growth factors through PRP to the site of repair to enhance native tendon healing. Further studies should focus on standardizing the preparation (i.e. leukocyte rich or poor) of PRP and delivery method in the setting of RCR. Double centrifugation, leukocyte poor preparation, and activation through calcium chloride treatment has been shown to have a reduction in retear rate (Walsh et al., 2018). Each study used calcium chloride or thrombin to activate the PRP solution prior to injection. Other methods such as sonication, light and electrical activation should also be investigated to further enhance the platelets' anabolic properties (Everts et al., 2020). If possible, an effort should be made to analyze the PRP solutions after collection to better understand the properties of the injected substance. Beyond utilizing optimal preparation methods, new biomaterial vehicles of delivery are being developed, such as Low-Molecular-Weight

Fucoidan-Functionalized Poly(Ester-Urea-Urethane) Scaffolds, that can be improve bioactivation of both PRP and the surrounding native tissue (Rohman et al., 2019).

Methods, such as autologous adipose-derived mesenchymal stem cell harvesting, may require additional planning for both the surgeon and the patient. Within the last 10 years, our understanding of processing, delivering and harvesting these biologic injectables has vastly improved. As researchers and clinicians look forward, it is important to begin consolidating methods to determine the current standard of injectable administration for each biologic. In the future, more standardization and clinical trials may lead to additional evidence supporting uniform injectable biologic solutions in RCR.

Marrow Induction

Recent advances in microfracture and marrow venting have demonstrated favorable results in both preclinical and clinical settings in an effort to improve biologic healing in primary rotator cuff repair. Preclinically, the results were promising and demonstrated improved histology (e.g., thicker collagen bundles) and improved load characteristics. Clinically, marrow stimulation has most often been employed in primary repair in the setting of large tears and has demonstrated variable but positive benefit. Three studies evaluated the effect of marrow stimulation in a medialized, single row repair with this technique demonstrating a very high healing rate in primary RCR. Furthermore, one study showed a statistically significant lower retear rate with single-row with microfracture versus single row and double row without microfracture (Jo et al., 2013).

Thus, microfracture techniques may be considered as a relatively straightforward technique to increase healing and potentially prevent retear.

Vented anchors have shown limited clinical benefit relative to their non-vented counterparts. Though the theoretical mechanism behind vented anchors is similar to that of marrow stimulation, the four papers included in this study demonstrated that vented anchors provided no clear benefit over non-vented anchors in either functional outcomes or retear rate at both short-term and long-term follow-up (Chahla et al., 2020; J.-H. Kim et al., 2020; Ro et al., 2019; Sarmento et al., 2019). Though two studies demonstrated that vented anchors improved ossification, bone mineral density, and bone mineral mass at the anchor-site, this did not translate to any meaningful difference in clinically significant outcomes (Chahla et al., 2020; J.-H. Kim et al., 2020).

Despite promising results, it should be noted that the local, procedural marrow-derived augmentation techniques discussed may not be feasible in all primary cases. Osteoporosis has been demonstrated to be an independent risk factor for failure of arthroscopic rotator cuff repair, potentially driven by the lower pullout strength in osteoporotic bone versus healthy bone (Chung et al., 2011; Pietschmann et al., 2010). Similarly, poor bone quality or small tear size may serve as barriers to implementation of microfracture techniques. In both cases, such procedures may compromise healing by weakening the bone and reducing stability at the anchor site, resulting in bone collapse or anchor loosening (Milano et al., 2013; Osti et al., 2013).

Limitations

A limiting factor of this review was the exclusion of studies with 1-year follow-up which may have limited the breadth of comprehensiveness of this review. However, a minimum 2-year follow-up was selected as an inclusion criterion in concordance with historical standard. Recent research has demonstrated that patient-reported outcomes may not significantly change between 1-year versus 2-year follow-up (Mahendraraj et al., 2021). This correlates with evidence already included in this review, such as the lack of significant difference in PROMs between 1-year and 2-year follow-up observed in porcine small intestinal mucosa augmentation (Bryant et al., 2016). In preclinical studies, a major limitation is the short follow-up due to use of animal models or cadavers. Many of the preclinical studies show promising results but do not translate into clinical studies beyond 3 months. This should be heavily considered, and the results of preclinical studies should be taken with caution in orthopedics because rotator cuff repair require long-term performance in real life. Another limitation of this review was that while our review was comprehensive upon injectables studied for repair, select injectables that do not have strong evidence investigating rotator cuff repairs but have been shown to affect the supraspinatus tendon were excluded from our review but may still warrant attention. Additionally, there is a large variability in preparation and source of injectable biologics coupled with a small sample size of clinical studies which may contribute to result heterogeneity (Parisien et al., 2021). Despite this relatively limited evidence, RCR augmentation with injectable biologics remains a promising avenue of improving patient outcomes.

CONCLUSION

The failure rate of standard arthroscopic rotator cuff repair varies between 11-94%. Advances in repair techniques have improved structural integrity, but biologic healing remains a significant challenge. Recent advances in 1. Grafts and scaffolds, 2. Injectable therapies, and 3. Microfracture and marrow venting have helped promote the biologic milieu and demonstrate favorable results in both preclinical and clinical settings.

Clinically, scaffolds have proven to be safe and effective in treating rotator cuff tears, offering a promising means to improve rotator cuff repair load-to-failure, stiffness, and strength. Incorporation of injectable biologics into RCRs has shown the potential for enhanced healing of the biologic intra/extra cellular environment. There are a wide range of biologic compositions, preparation processes, and delivery methods in use. Preclinically, growth factors and both adipose and bone marrow derived MSCs show the most promise in increasing load to failure and improving tendon histology. PRP and adipose-derived mesenchymal stem cells have shown positive effects such as lower retear rates along with improved VAS and SANE scores in the clinical setting. Though additional clinical data is needed, pre-clinical and clinical studies suggest injectable biologics may improve tendon quality and patient outcomes. Recent advances in marrow stimulation promote the biologic milieu and demonstrate favorable outcomes and limited adverse effects in both preclinical and clinical settings. Current evidence demonstrates that microfracture and marrow-venting techniques may have a positive impact on healing and retear rate, while vented anchors have muted impact relative to non-vented anchors. Though available evidence is limited and more research is needed, findings to date suggest marrow stimulation techniques may be an inexpensive, simple technique to consider in qualifying patients to prevent rotator cuff retears.

The data from this systematic review may prove valuable in terms of improving quality of care and prevention of retears. Given the onus of prevention of retear on the surgeon, surgeons must anticipate patients at risk of retear and work with payors to leverage technologies that improve healing and reduce retear rates in order to improve the value of care given. In the era of bundled payments, further consideration must be given to the relative cost-effectiveness of augmentation techniques. Increased healing and reduced retear via differing augmentations may result in cost-savings through avoidance of revision repair or the development of chronic tears, despite an increased time-zero cost associated with implementation of a unique technology or technique. Future direction includes larger trials with both radiographic and clinical follow-up for evaluation of lasting treatment effects, as well as cost-effectiveness analyses of newer marrow augmentation techniques and technologies.

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