Level V Evidence

Nonoperative and Operative Soft-Tissue, Cartilage, and Bony Regeneration and Orthopaedic Biologics of the Shoulder: An Orthoregeneration Network (ON) Foundation Review

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Abstract: Orthoregeneration is defined as a solution for orthopaedic conditions that harnesses the benefits of biology to improve healing, reduce pain, improve function, and optimally, provide an environment for tissue regeneration. Options include drugs, surgical intervention, scaffolds, biologics as a product of cells, and physical and electro-magnetic stimuli. The goal of regenerative medicine is to enhance the healing of tissue after musculoskeletal injuries as both isolated treatment and adjunct to surgical management, using novel therapies to improve recovery and outcomes. Various orthopaedic biologics (orthobiologics) have been investigated for the treatment of pathology involving the shoulder including the rotator cuff tendons, glenohumeral articular cartilage, glenoid labrum, the joint capsule, and bone. Promising and established treatment modalities include hyaluronic acid (HA); platelet-rich plasma (PRP) and platelet rich concentrates (PRC); bone marrow aspirate (BMA) comprising mesenchymal stromal cells (MSCs alternatively termed medicinal signaling cells and frequently, misleadingly labelled "mesenchymal stem cells"); MSC harvested from adipose, umbilical, or placental sources; factors including vascular endothelial growth factors (VEGF), basic fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGFβ), bone morphogenic protein (BMP), and matrix metalloproteinases (MMPs); prolotherapy; pulsed electromagnetic field therapy; microfracture and other marrow-stimulation techniques; biologic resurfacing using acellular dermal allografts, allograft Achilles tendons, allograft lateral menisci, fascia lata autografts, and porcine xenografts; osteochondral autograft or allograft); and autologous chondrocyte implantation (ACI). Studies involving hyaluronic acid, platelet rich plasma, and medicinal signaling cells of various origin tissues have shown mixed results to-date as isolated treatments and as surgical adjuncts. Despite varied results thus far, there is great potential for improved efficacy with refinement of current techniques and translation of burgeoning preclinical work. **Level of Evidence:** Level V, expert opinion.

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Introduction

Injury, disease, degeneration, and other damage to the tissues of the musculoskeletal system represent an immense and timeless burden for humans. The idea of tissue regeneration has been an aspirational goal to combat this burden dating back to the earliest civilizations.[1] In the recent past, attempts to harness modern biological and technological insights have led to a regenerative medicine revolution.[2] "Orthoregeneration" is a recently suggested term meant to encompass nonprosthetic procedures (drugs, surgical interventions, absorbable biomaterials, biologics, and physical and electromagnetic stimuli) to treat injured, diseased, or degenerated musculoskeletal tissues. Despite extraordinary advances, there remain many unknowns regarding these treatments. It is increasingly difficult for medical professionals, let alone patients, to stay abreast of the latest evidence and separate fact from fantasy. "Since 2017, the Orthoregeneration Network (ON) has served as an independent, international, nonprofit foundation driving development and understanding of new treatment options in the field of orthopaedic tissue regeneration. The mission of the ON is to provide guidance, education, and knowledge for surgeons to improve the use of tissue regeneration and biologic therapies in clinical practice."[3] The purpose of this edition of the *ON Foundation: Orthoregeneration Reviews* is to provide clinicians with an overview and assessment of the latest clinical evidence regarding regenerative treatments for ailments of the shoulder.

Overview of Orthoregeneration in the Shoulder

Shoulder pathology is one of the leading causes of pain and disability across the globe. Although the true prevalence of shoulder pathology is not known, authors have reported the annual incidence of shoulder pain in primary care at 14.7 per 1,000 patients per year with a lifetime prevalence of up to 70%.[4,5] The causes for shoulder pain and dysfunction are numerous. Excepting neurologic and/or functional disorders, all causes can be linked to an insult to, and/or degeneration of, the anatomic components of the shoulder. Damage to the tendons about the shoulder, chondral surfaces, subchondral bone, ligaments, and fibrocartilage structures (e.g., glenoid labrum) represent a broad spectrum of interrelated pathologies.[6]

Young, skeletally immature patients demonstrate a remarkable capacity for intrinsic healing.[7] On the other end of the spectrum, older adult patients with degenerative or traumatic shoulder injuries have experienced excellent outcomes following prosthetic shoulder implants.[8-10] This leaves a large percentage of the population who have poor intrinsic healing ability but are not yet optimal candidates for shoulder arthroplasty. Such patients stand to benefit immensely from advances in orthoregenerative techniques.

Herein, we will review the evidence for biological and orthoregenerative therapies in both the operative and nonoperative management of common shoulder pathologies. Specifically, we will focus on clinical evidence regarding platelet-rich plasma (PRP), hyaluronic acid (HA)-containing products, medicinal signaling cells (MSCs) of various cellular origins, and other related therapies. We will also comment on emerging trends and future directions in these areas.

Pathology of the Rotator Cuff Tendons

Accounting for upward of 5 million physician visits per year, rotator cuff disease is one of the most problematic orthopedic conditions.[11,12] Studies suggest at least 30% of people over the age of 60 will have full-thickness rotator cuff tears, and many more suffer from impingement and rotator cuff tendinopathy.[13] For many, these tears remain asymptomatic with little effect on quality of life; for others, significant pain and disability occur.

Many factors play a role in rotator cuff pathology. Mechanical impingement between the greater tuberosity of the humerus and underside of the acromion may initiate the inflammatory cascade, although this theory of disease is not definitive.[14] The rotator cuff's vascularity and healing potential are limited,[15] particularly at the anterolateral aspect of the footprint, where many tears are found or initiated. Suboptimal vascularity also limits access by signaling cells or growth factors that would otherwise guide a normal healing response favoring type I collagen produced by tenocytes. Whether in the setting of surgical or nonsurgical management, this can lead to the formation of biomechanically inferior fibrotic tissue, which can cause recurrent injury or poor response to treatment.[16-18] The rationale for biologic treatment of rotator cuff pathology, whether through changing the biological or structural milieu, is to guide the native rotator cuff away from tendinopathic changes and scar formation in favor of tenocyte formation and a physiological tendon-bone interface.

Orthoregenerative Treatments in Nonoperative Management

Traditional nonoperative management of rotator cuff disease includes activity modifications, physical therapy, anti-inflammatory medications, and corticosteroid injections. However, many patients derive limited or only short-term benefit from these modalities, and there is significant concern regarding the effects of repeated use of corticosteroid injections on tendon health.[19,20] Furthermore, whether because of concomitant health concerns or lifestyle implications, not all patients are good surgical candidates. For this

reason, orthoregenerative techniques have recently gained popularity—the three most common of which include PRP, MSCs, and prolotherapy.

Platelet-rich plasma and related products (platelet-rich concentrates [PRC]) are derived from an autologous, concentrated form of platelets and growth factors. Whole blood samples from the patient are centrifuged to concentrate the plasma layer, removing the red blood cell components with or without the white blood cell layer (buffy coat). The inclusion of the buffy coat (leukocyte rich) vs. exclusion (leukocyte poor) can be used for different injection sites depending on the type of pathology.[21] The concentrated delivery of growth factors that induce cellular migration, attracting various autologous stem cells and modulating the inflammatory response, is believed to be the primary mechanism of action.[22,23] The downregulation of specific inflammatory compounds, namely IL-6 and IL-8, has also been highlighted in the literature.[24]

Medicinal signaling cells, alternatively termed mesenchymal stromal cells (frequently and misleadingly referred to as "mesenchymal stem cells"), are commonly harvested and then concentrated from either bone marrow, adipose, umbilical, or placental sources.[25,26] These cells have been studied for their ability to differentiate into target tissues to aid in healing, while also altering the biological milieu.[27] Immunomodulation via suppression of inflammatory T-cells and monocyte maturation has been suggested.[28,29] Recent studies have also highlighted their ability to express potentially beneficial growth factors, such as transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF), both of which can aid in tissue healing.[29]

Prolotherapy involves injecting a natural irritant, often hypertonic dextrose, into the soft tissues to stimulate an inflammatory response that can trigger healing in pathologic tissues. Although the mechanism has not been completely elucidated, it is suggested that certain irritants can trigger the local release of growth factors and chemokines that ultimately modulate inflammation and trigger the production of the appropriate connective tissues.[30,31]

Various Level I randomized controlled studies have been performed for the aforementioned treatments (Table 1). The results for PRP for rotator cuff tendinosis or partial thickness tearing are mixed. In 2013, Kesikburum et al. reported no significant difference between PRP and normal saline injections for any patient-reported outcome (PRO) measured up to 1 year from the date of injection.[32] Similarly, Nejati et al. reported in 2016 that PRP was not better than exercise therapy for any measure after 6 months of therapy.[33] However, Sari et al. recently reported that for rotator cuff tendinosis, corticosteroid injections outperformed PRP for the visual analogue scale (VAS), American Shoulder and Elbow Surgeon's score (ASES), and Western Ontario Rotator Cuff Index (WORC) scores at 3 weeks, but at 24 weeks, patients who received PRP had better VAS and WORC scores.[34] Concerning partial-thickness rotator cuff tears, Cai et al. found that PRP was superior to placebo and hyaluronate injections for Constant scores after 12 months, while Ilhanli et al. found that, compared to physical therapy, PRP was superior for functional scores but not range of motion (ROM).[35,36]

Only one Level 1 randomized study was identified for MSCs in the nonoperative treatment of rotator cuff tears. Centeno et al., in 2020, found that the combined injection of bone marrow concentrate (BMC), PRP, and platelet lysate (PL) was superior to exercise programs alone at 3, 6, 12, and 24 months for pain and function.[37] In a prospective, nonrandomized study by Kim et al., it was reported that the combination of BMC and PRP was superior to exercise therapy alone for pain and function at 3 months for partial-thickness rotator cuff tears.[38]

Three Level I studies were identified for the use of prolotherapy to treat symptomatic supraspinatus tendinosis.[39-41] Bertrand et al. reported that dextrose-based prolotherapy was superior to saline placebo injection for pain and patient satisfaction after 9 months.[39] However, Lin et al. reported that while dextrose prolotherapy was superior at 2 weeks for pain and function compared to saline placebo, this effect waned after 6 weeks.[41] Finally, Cole et al. found that glucose-based prolotherapy was not superior to corticosteroids regarding pain and function at either 3 or 6 months from the date of injection.[40]

Orthoregenerative Treatments in Operative Management

Orthoregenerative treatments used in the operative setting are typically designed to augment or enhance the healing of native tendon to the bone and restore the physiological enthesis. Animal studies have suggested that tendon-to-bone healing following rotator cuff repair is histologically different from the preexisting enthesis.[42] Instead of the normal four transitional zones between tendon and bone, an abundance of scar tissue with type III collagen is formed.[17] While techniques using allograft or autograft patches are gaining interest in the structural augmentation of repair sites,[43-45] biologic approaches, including PRP, MSCs, and isolated growth factors, have been studied for orthoregenerative potential.[46]

Platelet-containing plasma derivatives, most notably PRP, are a popular option for biological augmentation of rotator cuff repair. As described above, platelets isolated in the plasma layer have been shown to release a host of cytokines and growth factors that can aid in tendon healing.[47] In addition to modulating the inflammatory response, these factors can recruit native

Table 1. Regenerative Therapy for Rotator Cuff Tendons: Nonoperative Studies Summary

Study	LOE	Year of Publication	Type of Intervention	Sample Size		Intervention Details		Follow-Up (months)	Favorable Outcome (Y/N)	Results Summary
				Test Group	Control	Test Group	Control			
Kesikburum et al.[32]	I	2013	PRP	20	20	PRP (1 injection)	Saline	12	N	No significant differences in PROs between groups at any time point.
Nejati et al.[33]	I	2017	PRP	31	31	PRP (2 injections over 1 month)	Exercise	6	N	Exercise group had significantly better improvement in various PROs, ROM, and strength parameters at 1, 3, and 6 months.
Sari et al.[34]	I	2020	PRP, dextrose prolotherapy	30	30 (prolotherapy); 30 (CSI); 30 (lidocaine)	PRP (1 injection)	1. CSI ; 2. prolotherapy; 3. lidocaine	6	Y	PRP group had significantly better VAS and WORC scores compared with the other groups at 6 months.
Cai et al.[35]	I	2019	PRP, SH	44 (SH); 45 (PRP); 48 (PRP + SH)	47	SH vs. PRP vs. PRP + SH (4 injections over 4 weeks for each)	Saline	12	Y	PRP + SH group had significantly better ASES, Constant, and VAS scores compared PRP, SH, or saline alone at 12 months.
Ilhanli et al.[36]	I	2015	PRP	30	32	PRP (3 injections over 3 weeks)	PT	12	Mixed	PT group had significantly better improvement in ROM compared with PRP group; PRP group had significantly better improvement in DASH scores compared with PT group at 12 months.
Centeno et al.[37]	I	2020	BMC + PRP + PL	14	11	BMC + PRP + PRP (1 injection)	Exercise	12	Y	Significant crossover. BMC group had significantly better improvement in NPS and SANE scores at 3 and 6 months.

(continued)

Table 1. Continued

Study	LOE	Year of Publication	Type of Intervention	Sample Size		Intervention Details		Follow-Up (months)	Favorable Outcome (Y/N)	Results Summary
				Test Group	Control	Test Group	Control			
Kim et al.[38]	II	2018	BMC + PRP	12	12	BMC + PRP (1 injection)	Exercise	3	Y	BMC group had significantly better improvement in VAS and ASES compared with the control group at 3 months.
Bertrand et al.[39]	I	2016	Dextrose prolotherapy	27	20 (deep); 27 (superficial)	25% dextrose (3 injections over 2 months)	1. deep saline injection; 2. superficial saline injection	9	Y	Dextrose group had significantly better improvement in pain scores and patient satisfaction compared with superficial saline injection group but not deep saline injection group at 9 months.
Cole et al.[40]	I	2018	Glucose prolotherapy	17	19	25% glucose (1 injection)	CSI	3	N	No significant differences in PROs between groups at any time point.
Lin et al.[41]	I	2019	Dextrose prolotherapy	16	15	40% dextrose (1 injection)	Saline	1.5	Mixed	Dextrose group had significantly better improvement in VAS, SPADI, and ROM compared with control group at 2 weeks but no difference at 6 weeks.

ASES, American Shoulder and Elbow Surgeon's score; BMC, bone marrow concentrate; CSI, corticosteroid injection; DASH, Disabilities of the Arm, Shoulder, and Hand; NPS, numeric pain scale; PL, platelet lysate; PROs, patient reported outcomes; PRP, platelet rich plasma; ROM, range of motion; PT, physiotherapy; SANE, single assessment numerical evaluation; SH, sodium hyaluronate; SPADI, Shoulder Pain and Disability Index; VAS, visual analog scale; WORC, Western Ontario Rotator Cuff index.

Table 2. Regenerative Therapy for Rotator Cuff Tendons: Operative Studies Summary

Study	LOE	Year of Publication	Type of Intervention	Sample Size		Intervention Details		Follow-Up (months)	Favorable Outcome (Y/N)	Results Summary
				Test Group	Control	Test Group	Control			
Atuna et al.[57]	I	2013	PRP	14	14	RCR + PRF injection intraoperatively	RCR	24	N	No significant differences in PROs between groups.
Castricini et al.[58]	I	2011	PRP	43	45	RCR + PRFM incorporated at repair site	RCR	16	N	No significant differences in PROs between groups, no significant difference in MRI-evaluated tendon healing between groups.
Malavolta et al.[59]	I	2014	PRP	27	27	RCR + PRP/autologous fibrin injection intraoperatively	RCR	24	Mixed	PRP group exhibited significantly better UCLA scores compared with control group at 12 months, all other PRO measures at all time points were nonsignificant.
Ruiz-Moneo et al.[60]	I	2013	PRP	32	31	RCR + PRP injection intraoperatively	RCR	12	N	No significant differences in PROs between groups, no significant difference in MRI-evaluated tendon healing between groups.
Wang et al.[61]	I	2015	PRP	30	30	RCR + PRP injections postoperatively at 7 and 14 days	RCR	4	N	No significant differences in PROs, ROM, strength, or MRI-evaluated tendon healing between groups.
Weber et al.[62]	I	2013	PRP	30	30	RCR + PRFM incorporated at repair site	RCR	12	N	Control group exhibited significantly better UCLA scores compared with PRFM group at 12 months; all other PROs, ROM, strength, and MRI-evaluated healing characteristics at all time points were nonsignificant.
Zumstein et al.[63]	I	2016	PRP	17	18	RCR + L-PRF clot incorporated at repair site	RCR	12	N	No significant differences in PROs and MRI-evaluated tendon healing between groups.
Flury et al.[64]	I	2016	PRP	60	60	RCR + PRP injection intraoperatively	RCR + ropivacaine injection intraoperatively	24	N	No significant differences in postoperative pain, PROs, or repair integrity between groups.
Snow et al.[65]	I	2020	PRP	40	47	RCR + LP-PRP injection postoperatively at 10-14 days	RCR + saline injection postoperatively at 10-14 days	12	N	No significant differences in PROs or retear rates as assessed by MRI between the groups at final follow-up.

(continued)

Table 2. Continued

Study	LOE	Year of Publication	Type of Intervention	Sample Size		Intervention Details		Follow-Up (months)	Favorable Outcome (Y/N)	Results Summary
				Test Group	Control	Test Group	Control			
Holtby et al.[55]	I	2016	PRP	41	41	RCR + PRP/autologous fibrin injection intraoperatively	RCR	6	Mixed	PRP group reported significantly less pain and painkiller consumption compared with control group within 30 days; all other PROs, ROM, and tendon healing parameters were not significantly different between groups.
Gumina et al.[56]	I	2012	P-L gel	39	37	RCR + P-L gel	RCR	13	Mixed	No significant differences in PROs between groups. Repair integrity significantly better in P-L group.
Kim et al.[66]	III	2017	a-MSC	35	35	RCR + a-MSC/fibrin glue injection intraoperatively	RCR	28	Mixed	No significant differences in PROs or ROM between groups. Presence of retearing on follow-up MRI significantly lower in a-MSC group compared with control.
Hernigou et al.[51]	III	2014	BMC	45	45	RCR + BMC injection intraoperatively	RCR	120	Y	BMC group demonstrated significantly greater healing rate by 6 months and had significantly lower rate of retearing on long-term surveillance MRI compared with control group.

a-MSC, adipose-derived mesenchymal stem cell; BMC, bone marrow concentrate; L-PRF, leucocyte and platelet rich fibrin; MRI, magnetic resonance imaging; P-L, platelet leukocyte; PRF, platelet rich fibrin; PRFM, platelet rich fibrin matrix; PROs, patient reported outcomes; PRP, platelet rich plasma; RCR, rotator cuff repair; UCLA, University of California, Los Angeles shoulder scores.

Table 3. Regenerative Therapy for Glenohumeral Articular Cartilage - Clinical Studies Summary

Study	LOE	Year of Publication	Type of Intervention	Adjunctive to Surgery (Y/N)	Sample Size		Intervention Details		Follow-Up (months)	Favorable Outcome (Y/N)	Results Summary
					Test Group	Control	Test Group	Control			
Centeno et al.[88]	III	2015	BMC + PRP + PL	N	115 (81 rotator cuff; 34 GH OA)	n/a	BMC + PRP + PL injection	n/a	11	n/a	Significant improvement in DASH, NPS, patient subjective improvement percentage between baseline and final follow-up.
Darrow et al.[87]	III	2019	WBM or BMC	N	50 (18 rotator cuff; 32 GH OA)	n/a	WBM or BMC injection	n/a	6	n/a	Significant improvement in resting pain, active pain, total improvement percentage, and functionality score between baseline and final follow-up.
Zhang et al.[83]	Meta-analysis of level I-IV studies	2019	HA	N	1,594	640	Various HA injection formulations	CSI, saline injection, or no control	Range 3-9	N	No significant differences in pain and functional outcomes between control and intervention arms.
Siebold et al.[94]	IV	2003	Microfracture	Y	5	n/a	Microfracture of humeral head with oversewn periosteal flap	n/a	26	n/a	Significant improvement in Constant and pain scores; radiographic osteoarthritis progression in 2 of 5 patients at final follow- up.
Millett et al.[92]	IV	2009	Microfracture	Y	24 (25 shoulders)	n/a	Microfracture of humeral head, glenoid, or both	n/a	47	n/a	Significant improvement in ASES score and other subjective measures between baseline and final follow-up; 19% rate of progression to further surgery.

(continued)

Table 3. Continued

Study	LOE	Year of Publication	Type of Intervention	Adjunctive to Surgery (Y/N)	Sample Size		Intervention Details		Follow-Up (months)	Favorable Outcome (Y/N)	Results Summary
					Test Group	Control	Test Group	Control			
Hünnebeck et al.[95]	IV	2017	Microfracture	Y	32	n/a	Microfracture of humeral head, glenoid, or both	n/a	105	n/a	Significant improvement in internal rotation from baseline to final follow-up; patients with osteoarthritis at baseline had significantly worse outcomes; 11% progression to arthroplasty.
Wang et al.[96]	IV	2018	Microfracture	Y	13 (14 shoulders)	n/a	Microfracture of humeral head, glenoid, or both	n/a	120	n/a	66.7% overall survival rate of intervention; significant improvements in SST and ASES between baseline and final follow up.
J. Frank et al.[93]	IV	2020	Microfracture	Y	16	n/a	Microfracture of humeral head, glenoid, or both	n/a	122	n/a	88% overall survival rate of intervention; significant improvements in multiple PRO measures between baseline and final follow-up.
Savoie et al.[101]	IV	2009	Biologic resurfacing	Y	20	n/a	Restore (DePuy Orthopaedics) patch sutured to glenoid surface	n/a	Range 36-72	n/a	75% overall survival rate of intervention; significant improvements in multiple PROs between baseline and final follow-up.
Hartzler et al.[100]	IV	2017	Biologic resurfacing	Y	43	n/a	GraftJacket MaxForce Extreme (Wright Medical) or Arthroflex (Arthrex) patch sutured to glenoid surface	n/a	60	n/a	23% rate of progression to arthroplasty; significant improvement in VAS pain, ASES, and ROM between baseline and final follow-up.

(continued)

Table 3. Continued

Study	LOE	Year of Publication	Type of Intervention	Adjunctive to Surgery (Y/N)	Sample Size		Intervention Details		Follow-Up (months)	Favorable Outcome (Y/N)	Results Summary
					Test Group	Control	Test Group	Control			
Strauss et al.[106]	IV	2014	Biologic resurfacing	Y	41	n/a	Lateral meniscal allograft or acellular dermal allograft patch (brand not reported)	n/a	34	n/a	51% clinical failure rate (45% for lateral meniscus, 70% for dermal allograft). Significant improvements in PROs at final follow-up compared to baseline.
Scheibel et al.[103]	IV	2004	Osteochondral autograft	Y	8	n/a	Autograft femoral condyle osteochondral plug to the humeral head or glenoid	n/a	33	n/a	Significant improvement in Constant score between baseline and final follow-up. Radiographic progression of osteoarthritic changes in 7 of 8 patients.
Riff et al.[102]	IV	2017	Osteochondral allograft	Y	18	n/a	Osteochondral allograft to the humeral head	n/a	67	n/a	Significant improvements in multiple PRO measures from baseline to final follow-up; 22% rate of conversion to arthroplasty at a mean of 25 months postoperatively.
Gobezie et al.[109]	IV	2016	Osteochondral allograft	Y	20	n/a	All-arthroscopic osteochondral allograft to the humeral head and glenoid	n/a	31	n/a	Significant improvements in multiple PRO measures from baseline to final follow up; 15% rate of conversion to arthroplasty at final follow-up.

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Table 3. Continued

Study	LOE	Year of Publication	Type of Intervention	Adjunctive to Surgery (Y/N)	Sample Size		Intervention Details		Follow-Up (months)	Favorable Outcome (Y/N)	Results Summary
					Test Group	Control	Test Group	Control			
Buchmann et al.[105]	IV	2012	ACI	Y	4	n/a	ACI to the humeral head or glenoid	n/a	41	n/a	Follow-up MRI demonstrated satisfactory defect coverage. No significance testing for preoperative vs postoperative PROs.
Boehm et al.[104]	IV	2020	ACI	Y	7	n/a	ACI to the humeral head	n/a	32	n/a	Complete coverage of defect found in 4 of 5 patients undergoing follow-up arthroscopy. Significantly improved SSV scores between baseline and final follow-up.

ASES, American Shoulder and Elbow Surgeons' score; BMC, bone marrow concentrate; CI, autologous chondrocyte implantation; CSI, corticosteroid injection; DASH, Disabilities of the Arm, Shoulder, and Hand; GH OA, glenohumeral osteoarthritis; HA, hyaluronic acid; NPS, numeric pain scale; PL, platelet lysate; PROs, patient reported outcomes; PRP, platelet rich plasma; ROM, range of movement; SST, simple shoulder test; SSV, Subjective Shoulder Value; VAS, visual analog scale; WBM, whole bone marrow.

stem cells to the repair site and stimulate blood vessel formation in an otherwise poorly vascularized area.[48] Certain growth factors, such as VEGF and hepatocyte growth factor (HGF), have previously been shown to guide tenocyte proliferation and increase the production of desired structural proteins, including type I collagen, decorin, aggrecan, and biglycan.[49]

Medicinal signaling cells can aid in tendon healing by either differentiating into tenocytes or osteoblasts at the repair site or guiding such differentiation from native progenitor cells.[50] Prior work has already demonstrated reduced progenitor cells at the tear site, highlighting the need for biological augmentation.[51] Human MSCs have been shown in vitro to differentiate into tenocytes in the appropriate biological milieu.[52] Autologous MSCs can be used either alone or with other growth factor preparations to guide the rotator cuff repair site toward the ideal tenogenic or osteogenic lineage.[53]

Many cytokines and growth factors are active at the rotator cuff repair site and can be supplemented to aid in tendon healing. Factors include vascular endothelial growth factors (VEGF), basic fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor-β (TGFβ), bone morphogenic protein (BMP), and matrix metalloproteinases (MMPs). These factors can increase angiogenesis to the repair site, increase cellular proliferation or tenocyte differentiation, promote bony incorporation at the tendon-bone junction, or remodel the tendon repair site favoring native type I collagen over scar formation.[54]

Outcomes regarding the use of orthoregenerative therapies in the operative treatment of rotator cuff repairs are mixed (Table 2). Holtby et al. found in 2016 that PRP augmentation for the repair of small or medium-sized rotator cuff tears helped with short-term perioperative pain but had no significant effect on PROs.[55] Gumina et al. also reported improved repair integrity, as measured by magnetic resonance imaging (MRI), in patients treated intraoperatively with a platelet-leukocyte (P-L) gel.[56] However, multiple Level I studies, whether the PRP was given intraoperatively or at various time intervals postoperatively, found that PRP had no significant effect on pain or any patient-reported outcome.[18,57-65]

Overall, there is a paucity of high-quality studies evaluating the use of MSCs to augment rotator cuff repairs. In one, Kim et al. showed MSCs derived from adipose tissue applied during arthroscopic single-row rotator cuff repair showed no clinical benefit, but drastically reduced retear rates at a 10-year follow up.[66] Another study by Hernigou et al. also found a significant decrease in retear rate, as measured by MRI, after surgical augmentation with MSCs derived from concentrated bone marrow.[67]

There is also a lack of high-quality investigation evaluating the use of isolated growth factors to augment rotator cuff repairs in humans. While the

application of VEGF to rat models of Achilles tendon repair was demonstrated to improve final tensile strength, no study has evaluated its use in humans.[68] Ide et al. reported that the application of FGF2 to rat model rotator cuff repairs accelerated bony ingrowth, but there was no difference in final repaired tendon strength.[69] Similarly, PDGF has been shown to increase the early tensile strength of rotator cuff repairs in sheep models, but there was no notable difference in ultimate tensile strength.[70] At this time, the use of isolated growth factors in the management of rotator cuff injuries is aspirational and requires further evaluation.

Articular Cartilage Pathology

Damage to the glenohumeral (GH) articular cartilage is a relatively common though underinvestigated entity when compared to similar ailments of the hip and knee.[71,72] Such damage may arise because of degeneration (primary arthritic change or secondary arthropathy), traumatic injury, inflammatory conditions, and/or iatrogenic injuries (prominent hardware from prior intervention, chondrolysis from intra-articular pain pumps).[73,74] Articular cartilage damage may be considered in varying degrees, from small, partial-thickness focal chondral defects up to widespread bipolar osteoarthritis (OA) affecting the subchondral bone.[75] Our understanding of the pathophysiology of articular cartilage damage and degeneration is evolving.[76] The main underlying challenge is that adult hyaline cartilage has a poor capacity for intrinsic healing.[77] As such, many efforts have been made to augment cartilage repair and regeneration in an effort to restore healthy hyaline cartilage. These efforts have mostly focused on aforementioned treatments such as PRP and MSCs.[78] For all degrees of symptomatic chondral pathology, the mainstay of initial treatment is nonoperative management. Efforts to augment nonoperative treatment with orthoregenerative approaches exist but have not been widely published in relation to GH chondral conditions.[79]

When nonoperative management fails, total shoulder arthroplasty (TSA) has proven to be an excellent option for older patients with OA. In younger patients, and/or in patients with early-stage pathology, reparative and restorative surgical techniques, such as microfracture, autologous chondrocyte implantation, and allograft resurfacing options have been described.[73] In an effort to improve the efficacy of these procedures, many have proposed the incorporation of biological adjuncts, though direct evidence is minimal, and most insights are extrapolated from efforts in other joints.[80]

Orthoregenerative Treatments in Nonoperative Management

Classically, nonoperative management for shoulder cartilage pathology has included activity modification, therapeutic exercise, oral anti-inflammatory medications, and injectable corticosteroid preparations. Orthoregenerative treatments may be used as adjuncts to these conservative measures, with the goal to engender a physiological healing response within the chondral tissue.

Viscosupplementation with exogenous high molecular-weight HA compounds has been trialed as a means of temporizing the degeneration of articular cartilage and restoring joint homeostasis. Hyaluronic acid is a naturally occurring molecule in cartilage and synovial fluid, which plays a role in regulation of the local tissue environment.[81] In degenerative states, endogenous HA is depolymerized to a low-molecular weight state, and its beneficial properties are diminished.[82] In 2019, Zhang et al. completed a meta-analysis on the outcomes of HA injections for GH OA; they reported on 15 studies involving 1,594 patients with levels of evidence ranging from I to IV (Table 3).[83] For the HA group, they found a significant pooled average reduction in VAS pain at 3 and 6 months following injection, as well as improvements on other validated PRO instruments. However, significant improvements were also found in the control groups across the included studies, which included corticosteroid and/or saline injections. These findings indicate that HA viscosupplementation is likely no better than existing treatment options.

Injectable MSC formulations from various sources are thought to play a key role in cartilage regeneration, given their potential for homing, self-renewal, and release of trophic factors that aid in tissue healing.[84] Furthermore, bone marrow aspirate (BMA)-derived MSC preparations contain anti-inflammatory cytokines and growth factors that are theorized to intervene in the cascade of inflammation and catabolism associated with degenerative cartilage pathology.[85,86] No randomized studies of MSC injections for GH cartilage damage have been published, although a few observational studies exist. In 2019, Darrow et al. reported on a cohort of patients treated with one or two injections of autologous bone marrow concentrate (BMC) or autologous whole bone marrow (WBM) for rotator cuff pathology or GH OA.[87] The OA cohort contained 32 patients evaluated at a mean follow-up of 6 months. In this group, VAS resting and active pain scores improved significantly from baseline to final follow-up, as did scores on an abridged version of the Upper Extremity Functional Index. The authors reported no significant differences in outcomes between the rotator cuff group and the isolated GH OA group. In another cohort study, Centeno et al. investigated the injection of BMC combined with PRP and PL into shoulders with rotator cuff injuries or GH OA.[88] Platelet lysate is obtained during the preparation of PRP by recentrifuging PRP and collecting a layer containing lysed platelets. Previous investigations have shown that the growth

Table 4. Regenerative Therapy for Adhesive Capsulitis: Clinical Studies Summary

Study	LOE	Year of Publication	Type of Intervention	Adjunctive to Surgery (Y/N)	Sample Size		Intervention Details		Follow-Up (months)	Favorable outcome (Y/N)	Results Summary
					Test Group	Control	Test Group	Control			
Kothari et al.[115]	I	2017	PRP	N	62	60 (CSI); 58 (ultrasonic therapy)	PRP (1 injection)	1. CSI; 2. ultrasonic therapy × 7 sessions	3	Y	Significantly better improvements in ROM, VAS pain, and QuickDASH for PRP vs. both comparator groups.
Barman et al.[114]	II	2019	PRP	N	28	27	PRP (1 injection)	CSI	3	Y	Significantly better improvements in VAS pain, SPADI, and ROM for PRP group.
Ünlü et al.[117]	I	2019	PRP	N	17	15	PRP (3 injections over 6 weeks)	Saline injections	3	Y	Significantly better improvements in VAS pain and disability and SPADI for PRP group.
Thu et al.[116]	I	2020	PRP	N	31	30	PRP (1 injection)	PT	1.5	N	No significant differences in VAS pain, DASH, and ROM between groups.

CSI, corticosteroid injection; DASH, Disabilities of the Arm, Shoulder and Hand; LOE, level of evidence; PRP, platelet rich plasma; PT, physiotherapy; ROM, range of motion; SPADI, Shoulder Pain and Disability Index; VAS, visual analog scale.

factors found in both PL and PRP can augment and enhance MSC proliferation in vitro.[89,90] The authors evaluated 115 shoulders in 102 distinct patients, of these, 34 shoulders had isolated GH OA. Between baseline and final follow-up (7-11 months), disabilities of the arm, shoulder and hand (DASH), and numeric pain scale (NPS) ratings improved significantly. No significant differences were found between the rotator cuff and isolated GH OA groups. As with the study by Darrow et al., this study did not include a control group and, therefore, no definitive conclusions can be made.

Orthoregenerative Treatments in Operative Management

Given that shoulder arthroplasty may be associated with suboptimal outcomes in younger patients with chondral defects or early-stage osteoarthritis,[91] the promise of orthoregenerative surgical intervention is attractive. At present, there are no high-level studies examining any orthoregenerative surgical techniques or adjuncts for GH cartilage pathology.

Microfracture and other marrow-stimulation techniques have been performed for small, contained chondral lesions and reported in a few case series (Table 3).[92-96] The aim of microfracture surgery is to stimulate bone marrow elements from the subchondral bone to deliver MSCs and growth factors to the chondral surface, where they will engender tissue healing and cartilage repair.[97] Despite the theoretical promise of this technique, the resulting fibrocartilage repair tissue has been shown to have suboptimal physiological and mechanical properties compared to native hyaline articular cartilage.[98,99] Although short to mid-term clinical improvements have been reported following microfracture for GH chondral lesions, long-term investigations report relatively high rates of OA progression and conversion to TSA.[95,96]

While marrow stimulation techniques are aimed at repairing small chondral defects, other modalities like biological resurfacing,[100,101] osteochondral grafting (autograft or allograft),[102,103] and autologous chondrocyte implantation (ACI),[104,105] are intended to restore articular cartilage in the setting of larger defects.

Biological shoulder resurfacing aims to remove damaged articular cartilage and replace it with an interpositional biological graft between the native humeral head (or a prosthetic humeral head) and the native glenoid. Various graft sources have been described, including acellular dermal allografts, allograft Achilles tendons, allograft lateral menisci, fascia lata autografts, and porcine xenografts, among others.[74] In 2009, Savoie et al. reported a case series of 23 patients treated with a porcine intestinal xenograft patch (Restore [DePuy Orthopedics, Warsaw, IN]) affixed to the glenoid surface.[101] The authors took samples and performed histological analyses showing that the patches

contained viable chondrocytes in a hyaline-like matrix at time 0, but no follow-up histological data were available. Clinically, the authors reported a 75% success rate for the procedure at 3-6 years follow-up, with significant improvements in ASES, VAS, Constant, Rowe, and University of California, Los Angeles (UCLA) shoulder scores. Hartzler et al. reported similar results in their 2017 study of 43 shoulders undergoing arthroscopic glenoid resurfacing with an acellular dermal allograft (GraftJacket MaxForce Extreme [Wright Medical, Arlington, TN], or Arthroflex [Arthrex Inc., Naples, FL]).[100] On the other hand, in 2014, Strauss et al. reported a high rate of clinical failure (51.2%) for either lateral meniscal allografts or acellular dermal allografts in biologic glenoid resurfacing among 41 patients followed for an average of 2.8 years.[106] Given the variable outcomes reported, biologic resurfacing is uncommon in clinical practice and requires further high-level investigation before conclusive comment on its regenerative efficacy is possible.

Osteochondral grafts seek to transfer a plug of viable osteochondral tissue, either from a deceased donor (allograft) or from a minimally weight-bearing chondral surface of the patient's body (autograft) to an area of focal chondral or osteochondral damage. These techniques are rarely used in the shoulder, but have shown good results when applied to defects in the knee.[107] Osteochondral grafts have the biologic advantage of restoring "like to like," as they implant a fully functional unit of osteochondral tissue that has the same physiological and mechanical properties as the surrounding joint surface. Small case series by Scheibel et al., evaluating osteochondral autografts, and Riff et al., evaluating osteochondral allografts, demonstrated varied results, with significant improvements in PRO measures, but relatively high rates of OA progression and conversion to TSA.[102,103] In 2016, Gobezie et al. reported on 20 patients undergoing bipolar osteochondral allografts of the humeral head and glenoid using an innovative all-arthroscopic technique[108] and found significant improvements in PRO and ROM outcomes at 2.5-year follow-up with a 15% rate of conversion to arthroplasty.[109]

Autologous chondrocyte implantation is a cell-based therapy for focal chondral defects that has mainly been used for cartilage pathology in the knee, although a few small investigations into its use in the shoulder have been reported.[104,105] Multiple iterations of ACI have been described, all of which involve taking a small biopsy of articular cartilage during an index procedure, expanding the cells ex vivo over a period of weeks, and then implanting the expanded cells back into the patient's chondral defect during a second procedure.[110] In a small case series by Boehm et al., 7 patients treated with ACI for chondral defects of the humeral head were followed for an average of 2.7 years.[104] They reported significant improvement in subjective shoulder value (SSV) scores at final follow-up and no relapse of focal chondral defects in 4 out of 5 patients who underwent second look arthroscopy. Although promising, no conclusions may be drawn, given the small sample size and observational nature of the investigation. There have been no clinical studies examining the efficacy of orthobiological treatments such as PRP and MSCs as adjuncts in the surgical management of GH pathology.

Other Shoulder Pathologies

Research relating to orthoregenerative treatments for other shoulder pathologies is similarly scarce. While labral and bony pathology associated with instability are common problems that receive much attention, most efforts in these areas aim at augmenting the pathologic anatomy in an effort to restore function, rather than regenerating the native anatomy.[111] Although an analysis of current procedural terminology code usage in a large database of American hospitals indicated that clinicians are performing PRP injections for patients with glenoid labral pathology, no clinical investigations into this practice have been published.[112]

Recently, some authors have investigated the use of orthoregenerative treatments in the nonoperative management of adhesive capsulitis (AC). The pathophysiology of AC involves inflammatory and fibrotic processes and cell signaling pathways, ultimately leading to hardening of the joint capsule, pain, and "frozen shoulder".[113] Understanding these pathophysiological underpinnings, several investigators have attempted to harness the anti-inflammatory properties of PRP in the treatment of AC (Table 4).[114-117] In 2017, Kothari et al. published results from a randomized study evaluating PRP vs. corticosteroid injection (CSI) vs. ultrasonic therapy for the nonoperative treatment of AC.[115] They found that patients in the PRP group had significantly greater improvements in VAS pain, QuickDASH, and ROM compared to the CSI and ultrasound groups at 12-week follow-up. Similarly encouraging short-term findings were published by Barman et al. in 2019, who found that patients treated with PRP had greater improvements in VAS pain, Shoulder Pain and Disability Index (SPADI), and ROM at 12 weeks compared to those treated with CSI.[114] Conversely, Thu and colleagues reported a randomized trial of PRP injection versus physiotherapy for AC and found no significant differences between the groups in VAS pain, DASH scores, and ROM after 6 weeks.[116] Further study in this area is needed to determine the long-term clinical efficacy of PRP injections, and also to characterize the physiological reaction to treatment in vivo.

Prospects for the Future

Although much investigation has been performed regarding orthoregenerative treatments for the rotator cuff, many unanswered questions remain. Further basic

scientific study is necessary to fully understand the biological underpinnings of both the pathology and the corresponding treatments. For example, recent strides have been made toward a greater understanding of the role of macrophages in the inflammatory response to tendon injury. As such, targeted therapeutics that influence this inflammatory milieu will likely become part of the armamentarium to combat rotator cuff disease.[118]

Clinically, additional high-level studies that focus on refining and standardizing the therapeutic indications, processing techniques, and timing of treatments are needed. Furthermore, efforts to augment existing cell-based therapies, such as BMA and other MSC preparations, with isolated growth factors may allow their regenerative potential to be fully harnessed.[119] Combining such treatments with structural biological scaffolds, such as those used in patch-augmented repairs and superior capsular reconstruction may further enhance their efficacy and improve anatomic results.[120] In addition to orthobiological modalities, adjuncts such as pulsed-electromagnetic field therapy may prove to be efficacious in promoting the healing and regeneration of rotator cuff tissue.[121] In contrast to the significant investigation into orthoregenerative treatments for the rotator cuff tendons, studies involving other commonly injured tissues of the shoulder are lacking. Investigators must adapt the promising work that has been undertaken in other joints in order to address similar pathology in the shoulder.

Conclusion

This review has highlighted the current clinical evidence for biological and orthoregenerative treatments for ailments of the shoulder. Much of the existing work in this area is focused on the rotator cuff tendons, with relatively few efforts directed toward other areas such as articular cartilage, labral, and bony pathology. Although the early evidence for treatments such as PRP and MSCs is varied, further efforts to refine and expand upon these modalities are needed to fully understand and harness the potential of orthoregeneration for the shoulder.

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