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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The authors report the following potential conflicts of interest or sources of funding: M.S. reports grants, personal fees and nonfinancial support from Arthrex, outside the submitted work. R.G. reports grants and personal fees from Arthrex, Inc., outside the submitted work. B.J.C. is a paid consultant for Acumed, LLC, Samumed, LLC, and Vericel Corporation. He reports research and financial support from Aesculap, research support from the National Institutes of Health, publishing royalties from Operative Techniques in Sports Medicine, *personal fees from Ossio and Regentis, financial and material support from Smith and Nephew, grants and personal fees from Arthrex, Inc., royalties from Elsevier Publishing, stock options from Bandgrip, Inc., financial support from Encore Medical, LP, GE Healthcare, Merck Sharp & Dohme Corporation, and SportsTek Medical, Inc., and Vericel Corporation, outside the submitted work. Full ICMJE author disclosure forms are available for this article online, as supplementary material.*

Received June 11, 2021; accepted June 16, 2021.

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0749-8063/21885

https://doi.org/10.1016/j.arthro.2021.06.033

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 signifiance 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.

Acknowledgments

The authors wish to acknowledge Kay Horsch, Ph.D. and Myron Spector, Ph.D., of the ON Foundation, for their collaboration in the conception of this review.

References

1. Horch RE, Popescu LM, Polykandriotis E. History of regenerative medicine. In: Steinhoff G, ed. *Regenerative medicine*. Dordrecht, Germany: Springer, 2011;1-17.
2. Noh MJ. Orthopedic cellular therapy: An overview with focus on clinical trials. *World J Orthoped* 2015;6:754.
3. Knapik DM, Evuarherhe AJ, Frank RM, et al. Nonoperative and operative soft-tissue and cartilage regeneration and orthopaedic biologics of the knee: An Orthoregeneration Network (ON) Foundation review. *Arthroscopy* In press.
4. Luime JJ, Koes BW, Hendriksen IJ, et al. Prevalence and incidence of shoulder pain in the general population: A systematic review. *Scand J Rheumatol* 2004;33:73-81.
5. van der Windt DA, Koes BW, De Jong BA, Bouter LM. Shoulder disorders in general practice: Incidence, patient characteristics, and management. *Ann Rheum Dis* 1995;54:959-964.
6. Lafosse L, Van Isacker T, Wilson JB, Shi LL. A concise and comprehensive description of shoulder pathology and procedures: The 4D code system. *Adv Orthop* 2012;2012:930543.
7. Soprano JV. Musculoskeletal injuries in the pediatric and adolescent athlete. *Curr Sports Med Rep* 2005;4:329-334.
8. Lo IK, Litchfield RB, Griffin S, Faber K, Patterson SD, Kirkley A. Quality-of-life outcome following hemiarthroplasty or total shoulder arthroplasty in patients with osteoarthritis. A prospective, randomized trial. *J Bone Joint Surg Am* 2005;87:2178-2185.
9. Mata-Fink A, Meinke M, Jones C, Kim B, Bell JE. Reverse shoulder arthroplasty for treatment of proximal humeral fractures in older adults: A systematic review. *J Shoulder Elbow Surg* 2013;22:1737-1748.
10. Samitier G, Alentorn-Geli E, Torrens C, Wright TW. Reverse shoulder arthroplasty. Part 1: Systematic review of clinical and functional outcomes. *Int J Shoulder Surg* 2015;9:24-31.
11. Day JS, Lau E, Ong KL, Williams GR, Ramsey ML, Kurtz SM. Prevalence and projections of total shoulder and elbow arthroplasty in the United States to 2015. *J Shoulder Elbow Surg* 2010;19:1115-1120.
12. Vitale MA, Vitale MG, Zivin JG, Braman JP, Bigliani LU, Flatow EL. Rotator cuff repair: An analysis of utility scores and cost-effectiveness. *J Shoulder Elbow Surg* 2007;16:181-187.
13. Lehman C, Cuomo F, Kummer FJ, Zuckerman JD. The incidence of full thickness rotator cuff tears in a large cadaveric population. *Bull Hosp Jt Dis* 1995;54:30-31.
14. McFarland EG, Maffulli N, Del Buono A, Murrell GA, Garzon-Muvdi J, Petersen SA. Impingement is not impingement: The case for calling it "Rotator Cuff Disease". *Muscles Ligaments Tendons J* 2013;3:196-200.
15. Laprade RF, Geeslin AG, Murray IR, et al. Biologic treatments for sports injuries II think tank—current concepts, future research, and barriers to advancement, part 1. *Am J Sports Sci* 2016;44:3270-3283.
16. Gulotta LV, Kovacevic D, Ehteshami JR, Dagher E, Packer JD, Rodeo SA. Application of bone marrow-derived mesenchymal stem cells in a rotator cuff repair model. *Am J Sports Med* 2009;37:2126-2133.
17. Kovacevic D, Rodeo SA. Biological augmentation of rotator cuff tendon repair. *Clin Orthop Relat Res* 2008;466:622-633.
18. Randelli P, Randelli F, Ragone V, et al. Regenerative medicine in rotator cuff injuries. *Biomed Res Int* 2014;2014:129515.
19. Dean BJ, Lostis E, Oakley T, Rombach I, Morrey ME, Carr AJ. The risks and benefits of glucocorticoid treatment for tendinopathy: A systematic review of the effects of local glucocorticoid on tendon. *Semin Arthritis Rheum* 2014;43:570-576.

20. Sherman SL, Khazai RS, James CH, Stoker AM, Flood DL, Cook JL. In vitro toxicity of local anesthetics and corticosteroids on chondrocyte and synoviocyte viability and metabolism. *Cartilage* 2015;6:233-240.
21. Lana JF, Huber SC, Purita J, et al. Leukocyte-rich PRP versus leukocyte-poor PRP. The role of monocyte/macrophage function in the healing cascade. *J Clin Orthop Trauma* 2019;10:S7-S12.
22. Pourcho AM, Smith J, Wisniewski SJ, Sellon JL. Intra-articular platelet-rich plasma injection in the treatment of knee osteoarthritis: Review and recommendations. *Am J Phys Med Rehab* 2014;93:S108-S121.
23. Schär MO, Diaz-Romero J, Kohl S, Zumstein MA, Nesic D. Platelet-rich concentrates differentially release growth factors and induce cell migration in vitro. *Clin Orthopaed Rel Res* 2015;473:1635-1643.
24. Andia I, Rubio-Azpeitia E, Maffulli N. Platelet-rich plasma modulates the secretion of inflammatory/angiogenic proteins by inflamed tenocytes. *Clin Orthopaed Rel Res* 2015;473:1624-1634.
25. Caplan AI. Mesenchymal stem cells: time to change the name! *Stem Cells Trans Med* 2017;6:1445-1451.
26. Rodeo S. Stem cells 101. *Am J Sports Med* 2021;49:1417-1420.
27. Menaa F, Shahrokhi S, Prasad Shastri V. Impact and challenges of mesenchymal stem cells in medicine: An overview of the current knowledge. *Stem Cells Int* 2018;2018:5023925.
28. Djouad F, Bouffi C, Ghannam S, Noel D, Jorgensen C. Mesenchymal stem cells: Innovative therapeutic tools for rheumatic diseases. *Nat Rev Rheumatol* 2009;5:392-399.
29. Freitag J, Bates D, Boyd R, et al. Mesenchymal stem cell therapy in the treatment of osteoarthritis: Reparative pathways, safety and efficacy. A review. *BMC Musculoskelet Disord* 2016;17:230.
30. DeChellis DM, Cortazzo MH. Regenerative medicine in the field of pain medicine: prolotherapy, platelet-rich plasma therapy, and stem cell therapy—Theory and evidence. *Tech Reg Anesth Pain Manag* 2011;15:74-80.
31. Hauser RA, Lackner JB, Steilen-Matias D, Harris DK. A systematic review of dextrose prolotherapy for chronic musculoskeletal pain. *Clin Med Insights Arthritis Musculoskelet Disord* 2016;9:139-159.
32. Kesikburun S, Tan AK, Yilmaz B, Yasar E, Yazicioglu K. Platelet-rich plasma injections in the treatment of chronic rotator cuff tendinopathy: A randomized controlled trial with 1-year follow-up. *Am J Sports Med* 2013;41:2609-2616.
33. Nejati P, Ghahremaninia A, Naderi F, Gharibzadeh S, Mazaherinezhad A. Treatment of subacromial impingement syndrome: Platelet-rich plasma or exercise therapy? A randomized controlled trial. *Orthop J Sports Med* 2017;5:2325967117702366.
34. Sari A, Eroglu A. Comparison of ultrasound-guided platelet-rich plasma, prolotherapy, and corticosteroid injections in rotator cuff lesions. *J Back Musculoskelet Rehabil* 2020;33:387-396.
35. Cai YU, Sun Z, Liao B, Song Z, Xiao T, Zhu P. Sodium hyaluronate and platelet-rich plasma for partial-thickness rotator cuff tears. *Med Sci Sports Exerc* 2019;51:227-233.
36. Ilhanli I, Guder N, Gul M. Platelet-rich plasma treatment with physical therapy in chronic partial supraspinatus tears. *Iran Red Crescent Med J* 2015;17. e23732.
37. Centeno C, Fausel Z, Stemper I, Azuike U, Dodson E. A randomized controlled trial of the treatment of rotator cuff tears with bone marrow concentrate and platelet products compared to exercise therapy: A midterm analysis. *Stem Cells Int* 2020;2020:5962354.
38. Kim SJ, Kim EK, Kim SJ, Song DH. Effects of bone marrow aspirate concentrate and platelet-rich plasma on patients with partial tear of the rotator cuff tendon. *J Orthop Surg Res* 2018;13:1.
39. Bertrand H, Reeves KD, Bennett CJ, Bicknell S, Cheng AL. Dextrose prolotherapy versus control injections in painful rotator cuff tendinopathy. *Arch Phys Med Rehabil* 2016;97:17-25.
40. Cole B, Lam P, Hackett L, Murrell GAC. Ultrasound-guided injections for supraspinatus tendinopathy: Corticosteroid versus glucose prolotherapy—a randomized controlled clinical trial. *Shoulder Elbow* 2018;10:170-178.
41. Lin CL, Huang CC, Huang SW. Effects of hypertonic dextrose injection in chronic supraspinatus tendinopathy of the shoulder: a randomized placebo-controlled trial. *Eur J Phys Rehabil Med* 2019;55:480-487.
42. Carpenter JE, Thomopoulos S, Flanagan CL, DeBano CM, Soslowsky LJ. Rotator cuff defect healing: a biomechanical and histologic analysis in an animal model. *J Shoulder Elbow Surg* 1998;7:599-605.
43. Avanzi P, Giudici LD, Capone A, et al. Prospective randomized controlled trial for patch augmentation in rotator cuff repair: 24-month outcomes. *J. Shoulder Elbow Surg* 2019;28:1918-1927.
44. Gilot GJ, Alvarez-Pinzon AM, Barcksdale L, Westerdahl D, Krill M, Peck E. Outcome of large to massive rotator cuff tears repaired with and without extracellular matrix augmentation: A prospective comparative study. *Arthroscopy* 2015;31:1459-1465.
45. Matthewson G, Coady CM, Wong IH-B. Rotator cuff reconstruction using fascia lata patch autograft for the nonrepairable rotator cuff tear. *Arthroscopy Techniques* 2020;9:e123-e130.
46. Lacheta L, Braun S. Limited evidence for biological treatment measures for cartilage and tendon injuries of the shoulder. *Knee Surg Sports Traumatol Arthrosc* In press.
47. Andia I, Sanchez M, Maffulli N. Platelet rich plasma therapies for sports muscle injuries: Any evidence behind clinical practice? *Expert Opin Biol Ther* 2011;11:509-518.
48. Hall MP, Band PA, Meislin RJ, Jazrawi LM, Cardone DA. Platelet-rich plasma: Current concepts and application in sports medicine. *J Am Acad Orthop Surg* 2009;17:602-608.
49. Jo CH, Kim JE, Yoon KS, Shin S. Platelet-rich plasma stimulates cell proliferation and enhances matrix gene expression and synthesis in tenocytes from human rotator cuff tendons with degenerative tears. *Am J Sports Med* 2012;40:1035-1045.
50. Murray IR, West CC, Hardy WR, et al. Natural history of mesenchymal stem cells, from vessel walls to culture vessels. *Cell Mol Life Sci* 2014;71:1353-1374.
51. Hernigou P, Merouse G, Duffiet P, Chevalier N, Rouard H. Reduced levels of mesenchymal stem cells at

the tendon-bone interface tuberosity in patients with symptomatic rotator cuff tear. *Int Orthop* 2015;39:1219-1225.
52. Mazzocca AD, McCarthy MB, Chowaniec D, et al. Bone marrow-derived mesenchymal stem cells obtained during arthroscopic rotator cuff repair surgery show potential for tendon cell differentiation after treatment with insulin. *Arthroscopy* 2011;27:1459-1471.
53. Costa-Almeida R, Calejo I, Gomes ME. Mesenchymal stem cells empowering tendon regenerative therapies. *Int J Mol Sci* 2019;20:3002.
54. Bedi A, Maak T, Walsh C, et al. Cytokines in rotator cuff degeneration and repair. *J Shoulder Elbow Surg* 2012;21:218-227.
55. Holtby R, Christakis M, Maman E, et al. Impact of platelet-rich plasma on arthroscopic repair of small- to medium-sized rotator cuff tears: A randomized controlled trial. *Orthop J Sports Med* 2016;4:2325967116665595.
56. Gumina S, Campagna V, Ferrazza G, et al. Use of platelet-leukocyte membrane in arthroscopic repair of large rotator cuff tears: A prospective randomized study. *J Bone Joint Surg Am* 2012;94:1345-1352.
57. Antuna S, Barco R, Martinez Diez JM, Sanchez Marquez JM. Platelet-rich fibrin in arthroscopic repair of massive rotator cuff tears: A prospective randomized pilot clinical trial. *Acta Orthop Belg* 2013;79:25-30.
58. Castricini R, Longo UG, De Benedetto M, et al. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: a randomized controlled trial. *Am J Sports Med* 2011;39:258-265.
59. Malavolta EA, Gracitelli ME, Ferreira Neto AA, Assuncao JH, Bordalo-Rodrigues M, de Camargo OP. Platelet-rich plasma in rotator cuff repair: A prospective randomized study. *Am J Sports Med* 2014;42:2446-2454.
60. Ruiz-Moneo P, Molano-Munoz J, Prieto E, Algorta J. Plasma rich in growth factors in arthroscopic rotator cuff repair: A randomized, double-blind, controlled clinical trial. *Arthroscopy* 2013;29:2-9.
61. Wang A, McCann P, Colliver J, et al. Do postoperative platelet-rich plasma injections accelerate early tendon healing and functional recovery after arthroscopic supraspinatus repair? A randomized controlled trial. *Am J Sports Med* 2015;43:1430-1437.
62. Weber SC, Kauffman JI, Parise C, Weber SJ, Katz SD. Platelet-rich fibrin matrix in the management of arthroscopic repair of the rotator cuff: A prospective, randomized, double-blinded study. *Am J Sports Med* 2013;41:263-270.
63. Zumstein MA, Rumian A, Thélu CÉ, et al. SECEC Research Grant 2008 II: Use of platelet- and leucocyte-rich fibrin (L-PRF) does not affect late rotator cuff tendon healing: a prospective randomized controlled study. *J Shoulder Elbow Surg* 2016;25:2-11.
64. Flury M, Rickenbacher D, Schwyzer H-K, et al. Does pure platelet-rich plasma affect postoperative clinical outcomes after arthroscopic rotator cuff repair? *Am J Sports Med* 2016;44:2136-2146.
65. Snow M, Hussain F, Pagkalos J, et al. The effect of delayed injection of leukocyte-rich platelet-rich plasma following rotator cuff repair on patient function: a randomized double-blind controlled trial. *Arthroscopy* 2020;36:648-657.
66. Kim YS, Sung CH, Chung SH, Kwak SJ, Koh YG. Does an injection of adipose-derived mesenchymal stem cells loaded in fibrin glue influence rotator cuff repair outcomes? A clinical and magnetic resonance imaging study. *Am J Sports Med* 2017;45:2010-2018.
67. Hernigou P, Flouzat Lachaniette CH, Delambre J, et al. Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: A case-controlled study. *Int Orthop* 2014;38:1811-1818.
68. Zhang F, Liu H, Stile F, et al. Effect of vascular endothelial growth factor on rat Achilles tendon healing. *Plast Reconstr Surg* 2003;112:1613-1619.
69. Ide J, Kikukawa K, Hirose J, et al. The effect of a local application of fibroblast growth factor-2 on tendon-to-bone remodeling in rats with acute injury and repair of the supraspinatus tendon. *J Shoulder Elbow Surg* 2009;18:391-398.
70. Kobayashi M, Itoi E, Minagawa H, et al. Expression of growth factors in the early phase of supraspinatus tendon healing in rabbits. *J Shoulder Elbow Surg* 2006;15:371-377.
71. Gartsman GM, Taverna E. The incidence of glenohumeral joint abnormalities associated with full-thickness, reparable rotator cuff tears. *Arthroscopy* 1997;13:450-455.
72. Paley KJ, Jobe FW, Pink MM, Kvitne RS, ElAttrache NS. Arthroscopic findings in the overhand throwing athlete: evidence for posterior internal impingement of the rotator cuff. *Arthroscopy* 2000;16:35-40.
73. McCarty LP, Cole BJ. Nonarthroplasty treatment of glenohumeral cartilage lesions. *Arthroscopy* 2005;21:1131-1142.
74. Cole BJ, Yanke A, Provencher MT. Nonarthroplasty alternatives for the treatment of glenohumeral arthritis. *J Shoulder Elbow Surg* 2007;16:S231-S240.
75. Bhosale AM, Richardson JB. Articular cartilage: structure, injuries and review of management. *Brit Med Bull* 2008;87:77-95.
76. Masson AO, Krawetz RJ. Understanding cartilage protection in OA and injury: A spectrum of possibilities. *BMC Musculoskel Disord* 2020:21.
77. Buckwalter J, Rosenberg L, Hunziker E. *Articular cartilage and knee joint function: Basic science and arthroscopy. Bristol-Myers/Zimmer Orthopaedic Symposium*. New York: Raven Press, 1990;19-56.
78. Rossi LA, Piuzzi NS, Shapiro SA. Glenohumeral osteoarthritis: The role for orthobiologic therapies: Platelet-rich plasma and cell therapies. *JBJS Rev* 2020;8:e0075.
79. Giotis D, Aryaei A, Vasilakakos T, Paschos NK. Effectiveness of biologic factors in shoulder disorders. *The Open Orthopaed J* 2017;11:163-182.
80. Southworth TM, Naveen NB, Nwachukwu BU, Cole BJ, Frank RM. Orthobiologics for focal articular cartilage defects. *Clin Sports Med* 2019;38:109-122.
81. Gupta RC, Lall R, Srivastava A, Sinha A. Hyaluronic acid: Molecular mechanisms and therapeutic trajectory. *Front Vet Sci* 2019;6:192.
82. Bowman S, Awad ME, Hamrick MW, Hunter M, Fulzele S. Recent advances in hyaluronic acid based therapy for osteoarthritis. *Clin Transl Med* 2018;7:6.

83. Zhang B, Thayaparan A, Horner N, Bedi A, Alolabi B, Khan M. Outcomes of hyaluronic acid injections for glenohumeral osteoarthritis: A systematic review and meta-analysis. *J Shoulder Elbow Surg* 2019;28:596-606.
84. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. *J Cell Biochem* 2006;98:1076-1084.
85. de Lange-Brokaar BJ, Ioan-Facsinay A, van Osch GJ, et al. Synovial inflammation, immune cells and their cytokines in osteoarthritis: A review. *Osteoarthritis Cartilage* 2012;20:1484-1499.
86. Kim GB, Seo M-S, Park WT, Lee GW. Bone marrow aspirate concentrate: Its uses in osteoarthritis. *Int J Mol Sci* 2020;21:3224.
87. Darrow M, Shaw B, Schmidt N, Boeger G, Budgett S, Schumacher U. Treatment of shoulder osteoarthritis and rotator cuff tears with bone marrow concentrate and whole bone marrow injections. *Cogent Med* 2019;6:1628883.
88. Centeno CJ, Al-Sayegh H, Bashir J, Goodyear S, Freeman MD. A prospective multi-site registry study of a specific protocol of autologous bone marrow concentrate for the treatment of shoulder rotator cuff tears and osteoarthritis. *J Pain Res* 2015;8:269-276.
89. Rubio-Azpeitia E, Andia I. Partnership between platelet-rich plasma and mesenchymal stem cells: In vitro experience. *Muscles Ligaments Tendons J* 2014;4:52-62.
90. Tavares MT, Santos SC, Custódio CA, Farinha JPS, Baleizão C, Mano JF. Platelet lysates-based hydrogels incorporating bioactive mesoporous silica nanoparticles for stem cell osteogenic differentiation. *Mater Today Bio* 2021;9:100096.
91. Schoch B, Schleck C, Cofield RH, Sperling JW. Shoulder arthroplasty in patients younger than 50 years: Minimum 20-year follow-up. *J Shoulder Elbow Surg* 2015;24:705-710.
92. Millett PJ, Huffard BH, Horan MP, Hawkins RJ, Steadman JR. Outcomes of full-thickness articular cartilage injuries of the shoulder treated with microfracture. *Arthroscopy* 2009;25:856-863.
93. Frank JK, Heuberer PR, Laky B, Anderl W, Pauzenberger L. Glenohumeral microfracturing of contained glenohumeral defects: Mid- to long-term outcome. *Arthroscopy* 2020;2:e341-e346.
94. Siebold R, Lichtenberg S, Habermeyer P. Combination of microfracture and periostal-flap for the treatment of focal full thickness articular cartilage lesions of the shoulder: A prospective study. *Knee Surg Sports Traumatol Arthrosc* 2003;11:183-189.
95. Hünnebeck SM, Magosch P, Habermeyer P, Loew M, Lichtenberg S. Chondral defects of the glenohumeral joint. *Obere Extremität* 2017;12:165-170.
96. Wang KC, Frank RM, Cotter EJ, et al. Long-term clinical outcomes after microfracture of the glenohumeral joint: Average 10-Year follow-up. *Am J Sports Med* 2018;46:786-794.
97. Salata MJ, Kercher JS, Bajaj S, Verma NN, Cole BJ. Glenohumeral microfracture. *Cartilage* 2010;1:121-126.
98. Nehrer S, Spector M, Minas T. Histologic analysis of tissue after failed cartilage repair procedures. *Clin Orthop Relat Res* 1999;365:149-162.
99. Gomoll AH, Minas T. The quality of healing: Articular cartilage. *Wound Repair Regenerat* 2014;22:30-38.
100. Hartzler RU, Melapi S, de Beer JF, Burkhart SS. Arthroscopic joint preservation in severe glenohumeral arthritis using interpositional human dermal allograft. *Arthroscopy* 2017;33:1920-1925.
101. Savoie FH, Brislin KJ, Argo D. Arthroscopic glenoid resurfacing as a surgical treatment for glenohumeral arthritis in the young patient: Midterm results. *Arthroscopy* 2009;25:864-871.
102. Riff AJ, Yanke AB, Shin JJ, Romeo AA, Cole BJ. Midterm results of osteochondral allograft transplantation to the humeral head. *J Shoulder Elbow Surg* 2017;26:e207-e215.
103. Scheibel M, Bartl C, Magosch P, Lichtenberg S, Habermeyer P. Osteochondral autologous transplantation for the treatment of full-thickness articular cartilage defects of the shoulder. *J Bone Joint Surg Br* 2004;86:991-997.
104. Boehm E, Minkus M, Scheibel M. Autologous chondrocyte implantation for treatment of focal articular cartilage defects of the humeral head. *J Shoulder Elbow Surg* 2020;29:2-11.
105. Buchmann S, Salzmann GM, Glanzmann MC, Wörtler K, Vogt S, Imhoff AB. Early clinical and structural results after autologous chondrocyte transplantation at the glenohumeral joint. *J Shoulder Elbow Surg* 2012;21:1213-1221.
106. Strauss EJ, Verma NN, Salata MJ, et al. The high failure rate of biologic resurfacing of the glenoid in young patients with glenohumeral arthritis. *J Shoulder Elbow Surg* 2014;23:409-419.
107. Capito NM, Owens BD, Sherman SL, Smith MJ. Osteochondral allografts in shoulder surgical procedures. *JBJS Rev* 2016:4.
108. Gobezie R, Lenarz CJ, Wanner JP, Streit JJ. All-arthroscopic biologic total shoulder resurfacing. *Arthroscopy* 2011;27:1588-1593.
109. Gobezie R, Shishani Y, Flocken J, Streit J, Carr RM. Two year results of all arthroscopic resurfacing of the glenohumeral joint with fresh osteochondral allograft: A prospective study. *J Shoulder Elbow Surg* 2016;25:e166.
110. Minas T, Chiu R. Autologous chondrocyte implantation. *Am J Knee Surg* 2000;13:41-50.
111. Rabinowitz J, Friedman R, Eichinger JK. Management of glenoid bone loss with anterior shoulder instability: Indications and outcomes. *Current Rev Musculoskelet Med* 2017;10:452-462.
112. Zhang JY, Fabricant PD, Ishmael CR, Wang JC, Petrigliano FA, Jones KJ. Utilization of platelet-rich plasma for musculoskeletal injuries. *Orthopaed J Sports Med* 2016;4:232596711667624.
113. Le HV, Lee SJ, Nazarian A, Rodriguez EK. Adhesive capsulitis of the shoulder: Review of pathophysiology and current clinical treatments. *Shoulder Elbow* 2017;9:75-84.
114. Barman A, Mukherjee S, Sahoo J, et al. Single intra-articular platelet-rich plasma versus corticosteroid injections in the treatment of adhesive capsulitis of the shoulder: A cohort study. *Am J Phys Med Rehabil* 2019;98:549-557.
115. Kothari SY, Srikumar V, Singh N. Comparative efficacy of platelet rich plasma injection, corticosteroid injection and ultrasonic therapy in the treatment of periarthritis shoulder. *J Clin Diagn Res* 2017;11:Rc15-rc18.

116. Thu AC, Kwak SG, Shein WN, Htun LM, Htwe TTH, Chang MC. Comparison of ultrasound-guided platelet-rich plasma injection and conventional physical therapy for management of adhesive capsulitis: a randomized trial. *J Int Med Res* 2020:48:030006052097603.
117. Ünlü B, Çalış FA, Karapolat H, Üzdü A, Tanıgör G, Kirazlı Y. Efficacy of platelet-rich plasma injections in patients with adhesive capsulitis of the shoulder. *Int Orthopaed* 2021;45:181-190.
118. Sunwoo JY, Eliasberg CD, Carballo CB, Rodeo SA. The role of the macrophage in tendinopathy and tendon healing. *J Orthopaed Res* 2020;38:1666-1675.
119. Cheung E. Delivered growth factor therapy to improve healing after rotator cuff repair. *Stem Cells Cloning* 2010;3:135-144.
120. Smith MJ, Bozynski CC, Kuroki K, Cook CR, Stoker AM, Cook JL. Comparison of biologic scaffolds for augmentation of partial rotator cuff tears in a canine model. *J Shoulder Elbow Surg* 2020;29:1573-1583.
121. Huegel J, Choi DS, Nuss CA, et al. Effects of pulsed electromagnetic field therapy at different frequencies and durations on rotator cuff tendon-to-bone healing in a rat model. *J Shoulder Elbow Surg* 2018;27:553-560.