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PROTEIN-RICH PLASMA: FROM BENCH TO TREATMENT OF ARTHRITIS (S CHOATE AND J TOKISH, SECTION EDITORS)

Current Clinical Recommendations for Use of Platelet-Rich Plasma

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Abstract

Purpose of Review This review evaluates current clinical literature on the use of platelet-rich plasma (PRP), including leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP), in order to develop evidence-based recommendations for various musculoskeletal indications.

Recent Findings Abundant high-quality evidence supports the use of LR-PRP injection for lateral epicondylitis and LP-PRP for osteoarthritis of the knee. Moderate high-quality evidence supports the use of LR-PRP injection for patellar tendinopathy and of PRP injection for plantar fasciitis and donor site pain in patellar tendon graft BTB ACL reconstruction. There is insufficient evidence to routinely recommend PRP for rotator cuff tendinopathy, osteoarthritis of the hip, or high ankle sprains. Current evidence demonstrates a lack of efficacy of PRP for Achilles tendinopathy, muscle injuries, acute fracture or nonunion, surgical augmentation in rotator cuff repair, Achilles tendon repair, and ACL reconstruction.

Summary PRP is a promising treatment for some musculoskeletal diseases; however, evidence of its efficacy has been highly variable depending on the specific indication. Additional high-quality clinical trials with longer follow-up will be critical in shaping our perspective of this treatment option.

Keywords Platelet-rich plasma · PRP · Orthobiologics · Regenerative medicine · Tendinopathy · Osteoarthritis

Introduction

Platelet-rich plasma (PRP) is a preparation of autologous human plasma with an increased platelet concentration produced by centrifuging a larger volume of a patient's own blood. Platelets contain a plethora of growth factors and mediators in their alpha granules (TGF-β1, PDGF, bFGF, VEGF, EGF, IGF-1), which are concentrated through the centrifugation process to release supraphysiologic amounts of these growth factors and cytokines to an injury site and augment the natural healing process [1–3, 4•]. The normal human platelet count ranges anywhere from 150,000 to 350,000/μL. Improvements in bone and soft tissue healing have been demonstrated with concentrated platelets of up to 1,000,000/μL, representing a three- to fivefold increase in growth factors [2, 5].

PRP preparations are typically further categorized into leukocyte-rich PRP (LR-PRP) preparations, defined as having a neutrophil concentration above baseline, and leukocyte-poor PRP (LP-PRP) preparations, defined as having a leukocyte (neutrophil) concentration below baseline.

Preparation and Composition

There is no general consensus on the optimal PRP preparation with respect to concentration of blood components and there are currently many different commercial PRP systems that are available on the market. As such, variation exists in the PRP collection protocols and preparation characteristics depending on the commercial system (Table 1), giving each PRP system unique properties [1, 8–10]. The commercial systems often

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Table 1 Commercially available PRP systems and their PRP preparations

System	Company	Blood volume required (mL)	Concentrated volume produced (mL)	Processing time (min)	PPP produced?	Increase in [platelets] (times baseline)	Platelet capture efficiency (% yield)
Leukocyte-rich PRP							
Angel	Arthrex	52 [6]	1–20[a]	17 [6]	+	10[a]	56–75% [6]
GenesisCS	EmCyte	54 [6]	6 [6]	10 [6]	+	4–7 [6]	61 ± 12% [6]
GPS III	Biomet	54 [6]	6 [6]	15 [6]	+	3–10 [6]	70 ± 30% [6]
Magellan	Isto Biologics/Arteriocyte	52 [6]	3.5–7 [6]	17 [6]	+	3–15 [6]	86 ± 41% [6]
SmartPReP 2	Harvest	54 [6]	7 [6]	14 [6]	+	5–9 [6]	94 ± 12% [6]
Leukocyte-poor PRP							
Autologous conditioned plasma (ACP)	Arthrex	11 [7]	4 [7]	5 [7]	–	1.3 [7]	48 ± 7% [7]
Cascade	MTF	18 [8]	7.5 [8]	6 [8]	–	1.6 [8]	68 ± 4% [8]
Clear PRP	Harvest	54[a]	6.5[a]	18[a]	+	3–6[a]	62 ± 5%[a]
Pure PRP	EmCyte	50[a]	6.5[a]	8.5[a]	+	4–7[a]	76 ± 4%[a]

[a] Data obtained from manufacturers' promotional literature or internal studies

differ in their platelet capture efficiency, isolation method (one- or two-step centrifugation), the speed of centrifugation, and the type of collection tube system and operation. Generally, whole blood is usually collected and mixed with an anticoagulant factor, prior to centrifugation, which separates red blood cells (RBCs) from platelet-poor plasma (PPP) and the "buffy coat," which contains the concentrated platelets and leukocytes. The platelets are isolated using various methods and can then be directly injected into the patient or be "activated" via the addition of either calcium chloride or thrombin, which then causes the platelets to degranulate and release the growth factors [2, 5]. Both patient-specific factors, including medications taken, and commercial system preparation methods influence the specific makeup of PRP, and this variability in the composition of PRP preparations creates challenges in interpreting the literature regarding the clinical efficacy of PRP [9–11].

Our current understanding is that PRP with elevated leukocyte content, that is, leukocyte (neutrophil)-rich PRP (LR-PRP), is associated with pro-inflammatory effects [9]. The elevated leukocyte (neutrophil) concentrations present in LR-PRP are also associated with elevated catabolic cytokines, such as interleukin-1β, tumor necrosis factor-α, and metalloproteinases, which may antagonize the anabolic cytokines contained within platelets [11]. The clinical ramifications and cellular effects of these different PRP preparations, including leukocyte content, are still currently being elucidated and this review seeks to evaluate the best quality evidence available for various clinical indications for different PRP preparations.

Treatment of Tendon Injuries

The treatment of tendon injuries or tendinopathies with PRP has been the subject of several studies (Table 2). Many of the cytokines found in PRP are involved in the signaling pathways that occur during healing stages of inflammation, cellular proliferation, and subsequent tissue remodeling [1, 2]. PRP may also promote neovascularization, which may increase the blood supply and nutrients needed for cells to regenerate the injured tissue as well as bring new cells and remove debris from damaged tissue. These mechanisms of action may be particularly relevant in chronic tendinopathies, where the biologic conditions are unfavorable for tissue healing. A recent systematic review and meta-analysis concluded that injections of PRP were efficacious for treatment of symptomatic tendinopathy [36•].

Lateral Epicondylitis

PRP has been evaluated as a potential treatment option for patients with lateral epicondylitis, who have failed to respond to physical therapy. In the largest such study, Mishra et al. evaluated 230 patients who failed to respond to at least 3 months of conservative treatment for lateral epicondylitis in a prospective cohort study [17•]. Patients were treated with LR-PRP and at 24 weeks, LR-PRP injection was associated with a significant improvement in pain compared to control (71.5% versus 56.1%, $P = 0.019$) as well as a significantly lower percentage of patients reporting residual elbow tenderness (29.1% versus 54.0%, $P = 0.009$). There was a clinically meaningful and statistically significant improvement at 24 weeks in patients treated with LR-PRP versus an active control injection of local anesthetic.

Previous studies have suggested that LR-PRP may also provide longer continuous relief of symptoms for lateral epicondylitis than corticosteroid injection and therefore have a more sustainable treatment effect [37, 38]. PRP appears to be an effective treatment for lateral

Table 2 Study design characteristics for PRP versus control injection for tendinopathies

				Sample size				Intervention/injection volume and contents			
Indication	Study	Year of publication	Level of evidence	PRP	Control	Type of PRP	Number of injections	PRP	Control	Follow-up (months)	Favors PRP?
Achilles tendinopathy	Boesen et al. [12•]	2017	I	20	20	LP-PRP	4	4 mL PRP + eccentric training	Sham injection + eccentric training	6	+
Achilles tendinopathy	Krogh et al. [13]	2016	I	12	12	LR-PRP	1	10–15 mL lidocaine → 6 mL PRP	10–15 mL lidocaine → 6 mL normal saline	3	–
Lateral epicondylitis	Behera et al. [14]	2015	I	15	10	LP-PRP	1	3 mL PRP + 0.5 mL calcium chloride	3 mL bupivacaine + 0.5 mL normal saline	12	+
Lateral epicondylitis	Gautam et al. [15]	2015	I	15	15	LP-PRP	1	2 mL PRP	2 mL methylprednisolone	6	+
Lateral epicondylitis	Lebiedzinski et al. [16]	2015	I	64	56	LP-PRP	1	3 mL PRP	1 mL betamethasone + 2 mL lidocaine	12	+
Lateral epicondylitis	Mishra et al. [17•]	2013	II	112	113	LR-PRP	1	Bupivacaine → 2–3 mL PRP	Bupivacaine → 2–3 mL bupivacaine	6	+
Lateral epicondylitis	Montalvan et al. [18]	2016	I	25	25	LP-PRP	2	2 mL lidocaine → 2 mL PRP	2 mL lidocaine → 2 mL normal saline	12	–
Lateral epicondylitis	Palacio et al. [19]	2016	I	20	20	LP-PRP	1	3 mL PRP	3 mL dexamethasone	6	–
Lateral epicondylitis	Yadav et al. [20]	2015	I	30	30	LR-PRP	1	1 mL PRP	1 mL methylprednisolone	3	+
Patellar tendinopathy	Dragoo et al. [21]	2014	I	10	13	LR-PRP	1	3 mL bupivacaine → 6 mL PRP + dry needling	3 mL bupivacaine + dry needling	6	+
Patellar tendinopathy	Vetrano et al. [22]	2013	I	23	23	NR	2	2 mL PRP	Extracorporeal shock wave therapy	12	+
Plantar fasciitis	Acosta-Olivo et al. [23]	2016	I	14	14	NR	1	3 mL of PRP + 0.45 mL of 10% calcium gluconate + lidocaine	2 mL dexamethasone + 2 mL of lidocaine	4	–
Plantar fasciitis	Jain et al. [24]	2015	I	30	30	LR-PRP	1	2.5 mL PRP	1 mL triamcinolone + levobupivacaine + sodium bicarbonate	12	–
Plantar fasciitis	Jain et al. [25]	2018	II	40	40	LR-PRP	1	2 mL lidocaine → 3 mL PRP	2 mL methylprednisolone + 2 mL lidocaine	6	–
Plantar fasciitis	Mahindra et al. [26]	2016	I	25	25	NR	1	2.5–3 mL PRP	2 mL methylprednisolone	3	+
Plantar fasciitis	Monto [27]	2014	I	20	20	LR-PRP	1	3 mL PRP + 6 mL bupivacaine	1 mL methylprednisolone + 6 mL bupivacaine	24	+
Plantar fasciitis	Say et al. [28]	2014	II	25	25	NR	1	2.5 mL of PRP + 5.5% calcium chloride	1 mL methylprednisolone + 1 mL of prilocaine	6	+
Plantar fasciitis	Sherpy et al. [29]	2015	I	25	25	LR-PRP	1	PRP + mepivacaine	1 mL triamcinolone + mepivacaine	3	–
Plantar fasciitis	Shetty et al. [30]	2014	II	30	30	LR-PRP	1	8 mL PRP	1 mL triamcinolone + 3 mL lidocaine	3	+
Plantar fasciitis	Tiwari et al. [31]	2013	I	30	30	LR-PRP	1	5 mL PRP	1 mL methylprednisolone + 1 mL prilocaine	6	+
Plantar fasciitis	Vahdatpour et al. [32]	2016	I	16	16	LR-PRP	1	3 mL PRP	1 mL methylprednisolone + 1 mL lidocaine	6	+
Rotator cuff tendinopathy	Kesikburun et al. [33]	2013	I	20	20	LR-PRP	1	1 mL lidocaine → 5 mL PRP	1 mL lidocaine → 5 mL normal saline	12	–
Rotator cuff tendinopathy	Rha et al. [34]	2013	I	20	19	LR-PRP	2	< 1 mL lidocaine → 3 mL PRP	< 1 mL lidocaine	6	+
Rotator cuff tendinopathy	Shams et al. [35]	2016	I	20	20	LP-PRP	1	2–2.5 mL PRP	5 mL triamcinolone	6	–

NR not reported, *LP-PRP* leukocyte-poor PRP, *LR-PRP* leukocyte-rich PRP, → denotes sequential injection

epicondylitis with high-quality evidence demonstrating short-term and long-term efficacy, and the best available evidence specifically suggest LR-PRP should be the treatment of choice [10•, 39, 40].

Patellar Tendinopathy

The use of LR-PRP to treat chronic refractory patellar tendinopathy has been supported by randomized controlled studies. Dragoo et al. evaluated 23 patients with patellar tendinopathy who had failed conservative management [21]. Patients were randomized to receive ultrasound-guided dry needling alone or with injection of LR-PRP and followed for > 26 weeks. The group treated with PRP has significant improvement in symptoms, as measured by VISA-P, at 12 weeks ($P = 0.02$) but the difference was not significant at > 26 weeks ($P = 0.66$), suggesting that the benefit of PRP for patellar tendinopathy may be earlier improvement of symptoms. Vetrano et al. also reported the benefit of PRP injections for treatment of chronic refractory patellar tendinopathy compared to focused extracorporeal shock wave therapy (ECSWT) [22]. While there was no significant difference between groups at 2-month follow-up, the PRP group showed statistically significant improvement, as measured by VISA-P and VAS, over ECSWT at 6-month and 12-month follow-up, and as measured by Blazina scale score at 12-month follow-up ($P < 0.05$ for all).

PRP appears to be a viable treatment option for chronic refractory patellar tendinopathy, and leukocyte-rich preparation is recommended. Given the small number of studies supporting this conclusion, further clinical trials will be necessary to recommend general clinical use.

Achilles Tendinopathy

Several historical trials failed to show a difference in PRP versus placebo injection in isolation to treat Achilles tendonitis in clinical outcomes [41, 42]. A more recent randomized controlled trial compared a series of four LP-PRP injections against placebo injection in combination with an eccentric loading rehabilitation program [12•]. The group treated with PRP had significantly improved pain, function, and activity scores at all time points throughout the 6-month follow-up period compared to the placebo group. This study also found a comparable improvement with a single high-volume injection (50 mL) of 0.5% bupivacaine (10 mL), methylprednisolone (20 mg), and normal saline (40 mL), although care should be taken when considering this treatment given the increase risk of tendon rupture after steroid injection. Ultimately, the routine use of PRP in Achilles tendinopathy is not supported by current literature.

Rotator Cuff Tendinopathy

There has been a paucity of high-level studies looking into PRP injections in the nonsurgical management of rotator cuff tendinopathy. The few studies that have been published have compared clinical outcomes of subacromial injection of PRP to placebo and corticosteroids, with no studies evaluating direct injection into the tendon itself. Kesikburun et al. found no difference in clinical outcome scores when compared to a subacromial injection of normal saline [33]. A randomized controlled trial, however, found that there was an improvement in pain with two injections of LR-PRP, separated 4 weeks apart, when compared with a placebo injection [34]. Shams et al. reported comparable improvements between subacromial PRP and corticosteroid injection in Western Ontario RC index (WORI), Shoulder Pain Disability Index (SPDI), and VAS shoulder pain with Neer test [35].

Studies to date have demonstrated equivocal improvement in patient-reported outcomes from subacromial injections of PRP for rotator cuff tendinopathy. Additional studies with longer follow-up are needed, to include evaluation of direct PRP injection into the tendon. These PRP injections have been shown to be safe and may be an alternative for corticosteroid injections in rotator cuff tendinopathy.

Plantar Fasciitis

Several randomized controlled trials have evaluated PRP injection in the management of chronic plantar fasciitis. The potential of PRP as a local injection treatment mitigates concerns associated with injection of corticosteroid, such as fad pad atrophy or plantar fascia rupture [43]. Two recent meta-analyses evaluated PRP injections against corticosteroid injections, concluding that PRP injections were a viable alternative to corticosteroid injections with respect to efficacy, with some studies demonstrating superiority of PRP [26•, 27, 28, 30, 32, 44, 45•]. Given the small sample sizes and limited number of high-quality RCTs, additional studies with more extensive follow-up are warranted.

PRP injections appear to be an effective treatment for improving pain and function in chronic plantar fasciitis and may be superior to corticosteroids, especially considering the improved safety profile of PRP.

Surgical Augmentation

Rotator Cuff Repair

Several high-level clinical studies have evaluated the use of PRP products as augments in arthroscopic repair of rotator cuff tears. Many of the studies specifically looked at the use of platelet-rich fibrin matrix preparation for augmentation

(PRFM) while others injected PRP directly into the repair site [46–48]. Significant heterogeneity of the PRP or PRFM preparations was present. Patient-directed outcomes, such as University of California-Los Angeles (UCLA), American Shoulder and Elbow Society (ASES), Constant Shoulder scores, Simple Shoulder Test (SST) scores, and VAS pain scores, were obtained, as well as objective clinical data such as rotator cuff strength and shoulder ROM have also been collected to measure functional outcome differences [47, 49–51]. The majority of individual studies have shown little difference in these outcome measures for PRP as an augment in arthroscopic rotator cuff repair compared to repair alone [46, 50, 52–55]. Additionally, large meta-analyses and a recent critical review demonstrated no significant benefit of PRP augmentation of arthroscopically repaired rotator cuffs [49, 56, 57•]. There was, however, limited data that showed some effect in reducing perioperative pain, which has been attributed most likely to PRP's anti-inflammatory properties [50, 54].

Subgroup analyses showed that better outcomes in the form of decreased re-tear rates with PRP injections may be achieved in small and medium tears treated with arthroscopic double-row repair [49, 55, 58]. Jo et al. found PRP to be beneficial in decreasing re-tear rates in medium and large rotator cuff tears versus surgery alone [47].

Randomized clinical trials and large meta-analyses demonstrate a lack of evidence for the use of PRP and PRFM as augmentation for rotator cuff repair. Some subgroup analyses suggest that there may be some benefits in small or medium tears, treated with double-row repair. PRP may also be beneficial in immediate postoperative pain reduction.

Achilles Tendon Repair

Preclinical studies have shown promising effects of PRP to augment healing in Achilles tendon ruptures [59–61]. Conflicting evidence however has prevented the translation of PRP as an effective adjunctive therapy for humans with acute Achilles tendon ruptures. For example, structural and functional results in patients with Achilles tendon ruptures surgically treated with and without addition of PRP were equivalent in one study [62]. In contrast, Zou et al. enrolled 36 patients in a prospective randomized controlled study who underwent repair of their acute Achilles tendon rupture with and without intraoperative LR-PRP injection [63]. Patients from the PRP group had better isokinetic muscle at 3 months and had higher SF-36 and Leppilahti scores at 6 and 12 months, respectively ($P < 0.05$ for all). In addition, ankle ROM was also significantly better in the PRP group at all time points of 6, 12, and 24 months ($P < 0.001$). Injection of PRP does not appear to be beneficial as a surgical augmentation for acute Achilles tendon repair, although more high-quality clinical trials are warranted.

Anterior Cruciate Ligament Surgery

The success of anterior cruciate ligament (ACL) surgery not only hinges on technical factors (e.g., graft tunnel placement and graft fixation) but also biologic healing of the ACL graft. Studies on the use of PRP in ACL reconstruction surgery have focused on three biologic processes: (1) osteoligamentous integration of the graft into the tibial and femoral tunnels, (2) maturation of the articular portion of the graft, and (3) and harvest site healing and pain reduction [64].

Though there have been multiple studies in the past looking at the use of PRP injections in ACL surgery, there has only been two high-level studies in the past 5 years. Past studies have shown mixed evidence supporting the use of PRP injections for osteoligamentous integration of the graft or graft maturation, but have shown some evidence to support its use in donor site pain [65–68]. With respect to augmentation with PRP to improve graft–bone tunnel incorporation, recent data has shown no clinical benefit of PRP in tunneling widening or osteointegration of the graft [69].

More recent clinical trials have shown promising early results on donor site pain and healing with the use of PRP. Seijas et al. looked at anterior knee pain after bone-patellar-bone (BTB) autograft ACL reconstruction and found decreased anterior knee pain at 2-month follow-up when compared to the control [70].

More studies are needed to investigate the effect of PRP on ACL graft integration, maturation, and donor site pain. However, at this time, studies have shown no significant clinical effect of PRP on graft integration or maturation, but limited studies have shown positive results in decreasing patellar tendon donor site pain.

Osteoarthritis

Osteoarthritis (OA) has unique characteristics with respect to joint biology, homeostasis, and levels of metalloproteases and inflammatory cytokines, contributing to patient symptoms [71]. Clinical reports on the use of PRP for cartilage injury have primarily involved patients with osteoarthritis of the knee or hip (Table 3).

Osteoarthritis of the Knee

There has been increased interest in the efficacy of PRP intra-articular injections for nonsurgical management of osteoarthritis of the knee [84]. Shen et al. performed a meta-analysis looking at 14 randomized clinical trials (RCTs), comprising of 1423 patients, comparing PRP to various controls including placebo, hyaluronic acid, corticosteroid injections, oral medications, and homeopathic treatments [85•]. The meta-analysis showed a significant improvement in Western

Table 3 Study design characteristics for PRP versus control injection for osteoarthritis

Indication	Study	Year of publication	Level of evidence	Sample size		Intervention/injection volume and contents				Follow-up (months)	Favors PRP?
				PRP	Control	Type of PRP	Number of injections	PRP	Control		
Hip osteoarthritis	Battaglia et al. [72]	2013	I	50	50	LR-PRP	3	5 mL PRP	30 mg HA	12	–
Hip osteoarthritis	Dallari et al. [73]	2016	I	44, +HA: 31	36	NR	3	7 mL PRP + HA	30 mg HA	12	+
Hip osteoarthritis	Doria et al.[74]	2017	II	40	40	NR	3	5 mL PRP	15 mg HA	12	–
Hip osteoarthritis	Sante et al. [75]	2016	I	21	22	NR	3	3 mL PRP	30 mg HA	4	+
Knee osteoarthritis	Cole et al. [76]	2017	I	49	50	LP-PRP	3	4 mL PRP	16 mg HA injection	12	+
Knee osteoarthritis	Duymus et al. [77]	2017	I	41	HA: 40, ozone: 39	NR	2	5 mL PRP	40 mg HA, 15 mL ozone	12	+
Knee osteoarthritis	Gormeli et al. [78]	2017	I	PRP (3×): 46, PRP (1×): 45	HA: 46, placebo: 45	NR	3 versus 1	5 mL PRP	30 mg HA, NR saline	6	+
Knee osteoarthritis	Lana et al. [79]	2016	I	36, +HA: 33	36	NR	3	5 mL PRP + 20 mg HA	20 mg HA	12	+
Knee osteoarthritis	Montanez et al. [80]	2016	I	28	27	NR	3	NR	NR HA	6	+
Knee osteoarthritis	Paterson et al. [81]	2016	I	12	11	NR	3	3 mL PRP	3 mL HA	3	–
Knee osteoarthritis	Simental et al. [82]	2016	I	33	32	LP-PRP	3	3 mL PRP	Tylenol 500 mg q8h	4	+
Knee osteoarthritis	Smith et al. [83•]	2016	I	15	15	LP-PRP	3	3–8 mL PRP	3–8 mL saline	12	+

NR not reported, *LP-PRP* leukocyte-poor PRP, *LR-PRP* leukocyte-rich PRP, *PRGF* plasma rich in growth factors, *HA* hyaluronic acid

Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores at 3-, 6-, and 12-month follow-up (= 0.02, 0.04, < 0.001 respectively). Subgroup analyses examining the efficacy of PRP based on severity of knee OA have shown PRP to be more effective in patients with mild to moderate OA [77–81]. Authors have suggested that intra-articular PRP injections are more efficacious in the treatment of knee OA, in terms of pain relief and patient-reported outcomes, than other alternative injections.

A meta-analysis by Riboh et al. compared LP-PRP and LR-PRP in the treatment of knee osteoarthritis and found that LP-PRP injections resulted in significantly improved WOMAC scores compared to HA or placebo [86•, 87–90]. Filardo et al. studied LR-PRP injections and alternatively found no statistical difference when compared to HA injections, providing further evidence that LP-PRP may be the preferred preparation for the treatment of osteoarthritis symptoms [65•, 91]. The biological basis for this may be in the relative level of inflammatory versus anti-inflammatory mediators present in LR-PRP and LP-PRP. Inflammatory mediators TNF-α, IL-6, IFN-ϒ, and IL-1β are increased significantly in the presence of LR-PRP, whereas injection of LP-PRP increases IL-4 and IL-10, which are anti-inflammatory mediators [11, 92, 93]. IL-10 specifically was found to be helpful in the treatment of hip osteoarthritis and may also suppress the release of the inflammatory mediators TNF-α, IL-6, and IL-1β, and block the inflammatory pathway by neutralizing nuclear factor-kB activity [11, 73, 82, 92, 94]. In addition to its deleterious effects on chondrocytes, LR-PRP may also fail to help treat osteoarthritis symptoms due to its effect on synoviocytes. Braun et al. found that treatment of synovial cells with LR-PRP or erythrocytes resulted in significant pro-inflammatory mediator production and cell death [95].

Intra-articular injection of LP-PRP is a safe treatment and there is level 1 evidence demonstrating its ability to reduce pain symptoms and increase function in patients diagnosed with osteoarthritis of the knee [83•, 85•]. Larger studies with longer follow-up are needed to determine its long-term efficacy.

Osteoarthritis of the Hip

There have only been four randomized clinical trials comparing PRP injections to hyaluronic acid (HA) injections for the treatment of hip OA. Outcome measures were VAS pain scores, WOMAC scores, and Hip Harris Scores (HHS).

Battaglia et al. found significant improvement in VAS score and HHS at the 1-, 3-, 6-, and 12-month marks. Peak improvement was seen at the 3-month mark with diminishing effect thereafter [72]. Scores at the 12-month mark remained significantly improved from baseline scores ($P < 0.0005$); however, there were no statistically significant outcome differences between the PRP and HA groups.

Di Sante et al. saw the PRP group's VAS scores significantly improve at 4 weeks, but return to baseline at 16 weeks [75]. The HA group showed no significant difference in VAS score at 4 weeks but a significant improvement at 16 weeks. Dallari et al. evaluated PRP against HA injections but also compared the combination of HA and PRP injected together to both injections alone [73]. The PRP group was found to have the lowest VAS score of all three groups at all (2-, 6-, and 12-month) follow-up time points. PRP also had a significantly better WOMAC score at 2 and 6 months but not at 12 months. Doria et al. performed a double-blinded randomized clinical trial comparing patients who received three consecutive weekly injections of PRP versus three HA injections [74•]. The study found improvement in HHS, WOMAC, and VAS scores at 6- and 12-month follow-up for both the HA and PRP groups. However, there was no significant difference between the two groups at all time points. None of the studies showed an adverse effect from intra-articular PRP injections into the hip and all concluded that PRP was safe.

Although the data is limited, intra-articular injection of PRP for osteoarthritis of the hip has shown to be safe and has some efficacy in pain reduction and improved function as measured by patient-reported outcome scores. Multiple studies have shown PRP to initially have a better pain reduction when compared to HA; however, any initial advantage seems to decrease over time with PRP and HA having very similar efficacy by 12 months. As there have been a small number of clinical studies evaluating the use of PRP for OA of the hip, more high-level evidence is needed to determine if PRP can be used as an alternative conservative treatment to delay surgery for osteoarthritis of the hip.

Ankle Sprains

Only two randomized clinical trials meeting our inclusion criteria evaluated the use of PRP in the setting of acute ankle sprains. Rowden et al. performed a double-blinded placebo-controlled randomized clinical trial of patients with acute ankle sprains in the ED comparing ultrasound-guided LR-PRP injections with local anesthetic versus injection of normal saline with local anesthetic [96]. They found that there was no statistical difference in the VAS pain score or Lower Extremity Functional Scale (LEFS) between the two groups.

Laver et al. randomized 16 elite athletes diagnosed with a high ankle sprain to treatment with either an ultrasound-guided LP-PRP injection at initial presentation with a repeat injection 7 days later in conjunction with a rehabilitation program or rehabilitation program alone, with all patients receiving the same rehabilitation protocol and return to play criteria [97]. The study found the LP-PRP group returned to play in a shorter amount of time (40.8 versus 59.6 days, $P < 0.006$).

PRP does not appear to be efficacious in the setting of acute ankle sprains. While limited evidence suggests LP-PRP injections may be helpful in high ankle sprains in elite athletes, the paucity of evidence leads us to conclude that PRP injections cannot be routinely recommended for high ankle sprains.

Muscle Injuries

The use of PRP in the treatment of muscle injuries has shown equivocal clinical evidence. Similar to tendon healing, the steps in muscle healing involve the initial inflammatory response, which is then followed by cell proliferation, differentiation, and tissue remodeling. Hamid et al. conducted a single-blind randomized study of 28 patients with grade 2 hamstring muscle injuries comparing an injection of LR-PRP with a rehabilitation program versus rehabilitation alone [98]. The group treated with LR-PRP was able to return to play faster (mean time in days, 26.7 vs. 42.5, $P = 0.02$), but structural improvements were not achieved. Additionally, significant placebo effect in the treatment arm may have confounded these results. In a double-blind randomized controlled trial, Reurink et al. evaluated 80 patients comparing PRP injections to placebo saline injections, with all patients receiving standard rehabilitation [99]. The patients were followed for 6 months and there were no significant differences in return to play time or with re-injury rate. The ideal formulation of PRP to improve muscle healing in a clinically relevant way continues to remain elusive and should be subject to future study.

Fracture and Nonunion Management

Despite reasonable preclinical evidence to support the use of PRP to improve bone healing, there is no clinical consensus to support the routine use of PRP to enhance bone healing [100–103]. A recent review of PRP and acute fracture treatment highlighted three RCTs that failed to show benefit in terms of functional outcomes, whereas two studies showed superior clinical outcomes [104]. The majority of trials in this review (6/8) studied the efficacy of PRP in conjunction with other biologics such as mesenchymal stem cells and/or bone graft to promote fracture healing. Therefore, we cannot yet recommend use of PRP in fracture care.

Conclusion and Summary of Recommendations

Platelet-rich plasma (PRP) works by delivering a supraphysiologic amount of growth factors and cytokines contained within platelets. In musculoskeletal medicine, PRP

is a promising treatment modality with clear evidence of safety. However, evidence of its efficacy has been mixed and highly dependent on composition and on the specific indication. Additional future high-quality, large clinical trials will be critical in shaping our perspective of PRP. The heterogeneity of PRP preparations, both presently and historically, has made interpreting the existing literature difficult and limits our ability to make definitive treatment recommendations.

Nonetheless, based on the current best available literature, the following recommendations are summarized: Abundant high-quality evidence supports the use of LR-PRP injection for lateral epicondylitis and LP-PRP for osteoarthritis of the knee. Moderate high-quality evidence supports the use of LR-PRP injection for patellar tendinopathy and of PRP injection for plantar fasciitis and donor site pain in patellar tendon graft BTB ACL reconstruction. There is insufficient evidence to routinely recommend PRP for rotator cuff tendinopathy, osteoarthritis of the hip, or high ankle sprains. Current evidence demonstrates a lack of efficacy of PRP for Achilles tendinopathy, muscle injuries, acute fracture or nonunion, surgical augmentation in rotator cuff repair, Achilles tendon repair, and ACL reconstruction.

Compliance with Ethical Standards

Conflict of Interest Dr. Dragoo reports consultancy for Ossur, Genzyme, Depuy/Mitek, Linvatec, Miximed, Zimmer, Harvet/Terumo, and Flexion Therapeutics, grants from Ossur, and educational funding from Linvatec, Smith and Nephew, Breg, and Ossur. All other authors declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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