Chapter 5
Platelet-Rich Plasma

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Introduction

In 2001, Dr. Richard Marx, an oral and maxillofacial surgeon, defined platelet-rich plasma (PRP) as a "volume of autologous plasma that has a platelet concentration above baseline" [1]. However, surgical applications of platelets and clotting factors, fibrinogen and thrombin, emerged much earlier in the 1970s and 1980 to augment healing. Yet, it was not until Dr. Marx's publication that a catalyst was in place for the development of PRP technology and commercialization.

By 2008, Hines Ward, then wide receiver for the Pittsburgh Steelers, reported to the media that he received PRP treatment for an acute grade 2 medial collateral ligament sprain, allowing him to return to play within 2 weeks, compared to the more typical 4–6-week recovery period [2]. The Steelers went on to win the Super Bowl that year. Ward's injury, treatment, and response to PRP therapy represents a key event and impetus for growing clinical interest in PRP applications in sports medicine and musculoskeletal injuries.

In this chapter, we discuss the basic science underlying PRP and clinical applications for musculoskeletal pathology. We review the diverse classification schemes and preparation methods of PRP, which relate to observed variations in clinical outcomes and efficacy of treatment, and the advantages and disadvantages of PRP therapy. We examine the regulation of PRP technology and barriers to expanding Food and Drug Administration approval for additional musculoskeletal indications. Finally, we close with future directions for PRP applications to the field of nonoperative sports medicine and spine care.

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Basic Science of PRP and Mechanism of Action

Clinical interest in PRP lies in its regenerative properties, as well as its anti-inflammatory, anti-microbial, and analgesic actions on the tissue of interest [3]. Platelets are anucleate cytoplasmic fragments of megakaryocytes from the bone marrow, containing upward of 50–80 α-granules per platelet [4]. Physiological levels of platelets range from 150,000 to 350,000/μL. Their lifespan is approximately 10 days in circulation [5], and platelet death occurs by an intrinsic program of apoptosis [6]. Platelet activation, adhesion, and aggregation are the initial steps of the wound repair process and inflammatory cascade (Fig. 5.1). After activation, α-granules within the platelets degranulate, releasing growth factors and cytokines involved in cell proliferation and tissue remodeling, which play key roles in wound healing and repair.

The composition of PRP has been reported to contain over 300 growth factors and cytokines [8]. Growth factors present in PRP are promoters of mitogenesis and anabolism and have also been shown to suppress inflammation [9]. For example, PRP contains growth factors that have been shown to enhance chondrocyte proliferation, extracellular matrix (ECM) synthesis, and mesenchymal differentiation in laboratory studies [10, 11]. These growth factors include platelet-derived growth factors (PGDF-AA, PDGF-AB, PDGF-BB), transforming growth factors (TGF-β1,

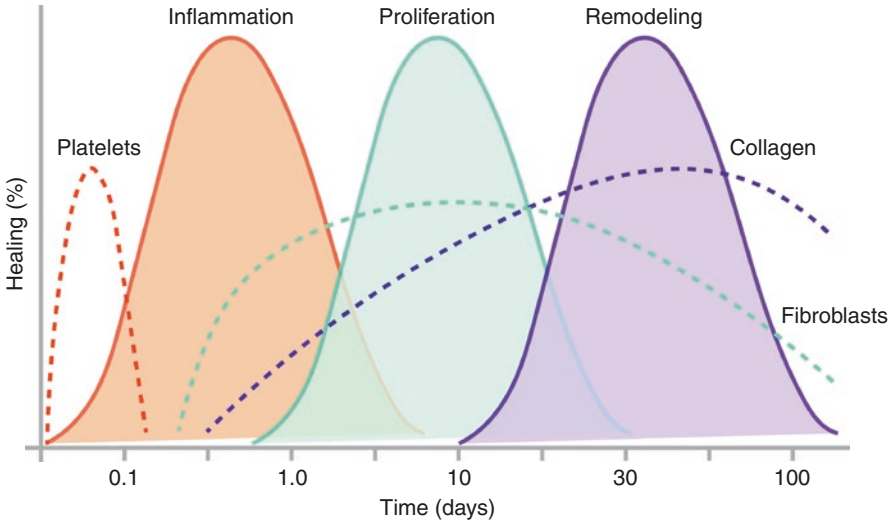

Fig. 5.1 The three overlapping phases of wound healing: inflammation, proliferation, and remodeling. Following tissue injury, platelet adhesion, aggregation, and activation occur, along with initiation of the inflammatory cascade, occurring over the first few days of healing. This is followed by the cell proliferation and tissue synthesis phase, consisting of angiogenesis, collagen deposition, granulation tissue formation, epithelization, and wound contraction. Finally, the tissue remodeling phase occurs weeks to months after injury, involving collagen and extracellular matrix maturation. Time in days presented on a logarithmic scale. (Modified from Lee et al. [7])

TGF-β2), insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and fibroblast growth factor β (FGF-β) [1, 9]. PDGF in PRP has a role in early wound healing and stimulates fibroblast proliferation [12]. TGF-β1 increases collagen production by fibroblasts [13]. PRP also comprises cytokines with pro-inflammatory (interleukin 1, interleukin 6) and anti-inflammatory (interleukin 4, interleukin 10) functions. The function of major growth factors and cytokines of relevance to wound healing is summarized in Table 5.1.

Table 5.1 Composition of PRP and selected growth factors and cytokines involved in wound healing, musculoskeletal repair and regeneration

Growth factor or cytokine[a]	Role(s) in wound healing, musculoskeletal repair, and regeneration[a]	Reported concentrations in PRP	
		PRP system[b]	Concentration
Ang-2	Angiogenesis; chondrogenic and osteogenic differentiation [15–17]	PCCS	425 ± 405 pg/mL [18]
EGF	Endothelial chemotaxis and angiogenesis; MSC and epithelial cell mitogenesis; collagen synthesis; osteogenic and chondrogenic differentiation of MSCs [19, 20]	Arthrex	659.8 ± 35.9 pg/mL [4]
		Fibrinet	1.4 ± 1.2 ng/mL [21]
		GPS	470 ± 317 pg/mL [22]
		GPS III	2639.5 ± 197.7 pg/mL [23]
		PCCS	57 ± 77 pg/mL [18]
		Plateltex	1.6 ± 0.7 ng/mL [21]
		Regen	0.1 ± 0.1 ng/mL [21]
bFGF	MSC, chondrocyte, osteoblast, and capillary endothelial cells mitogenesis; chondrocyte, myoblast, and osteoblast differentiation [24, 25]	Arthrex	15.6 ± 2.4 pg/mL [23]
		Fibrinet	31 ± 27 pg/mL [21]
		GPS III	75.2 ± 21.4 pg/mL [23]
		Plateltex	3.5 ± 8 pg/mL [21]
		Regen	13 ± 10 pg/mL [21]
HGF	Angiogenesis, endothelial cell mitogenesis; anti-inflammatory effects [26]	Arthrex	645.2 ± 72.1 pg/mL [23]
		GPS III	4277.3 ± 1508.2 pg/mL [23]
IGF-1	Myoblast proliferation and differentiation; fibroblast chemotaxis and protein synthesis; osteoblast proliferation and differentiation; MSC proliferation and survival [27, 28]	AGF	132 ± 32 ng/mL [29]
		Arthrex	64.8 ± 55.4 pg/mL
		CS	100 ± 29 ng/mL [29]
		Fibrinet	27 ± 11 ng/mL [21]
		GPS	72 ± 25 pg/mL [22] 99 ± 29 ng/mL [29]
		GPS III	672.9 ± 378.4 pg/mL [23]
		MCS 3p	84 ± 23 ng/mL [30]
		PCCS	5.550 ± 2.075 ng/mL [18]
		Plateltex	88 ± 34 ng/mL [21]
		Regen	36 ± 14 ng/mL [21]
IL-1	Pro-inflammatory and catabolic effects [31]	Arthrex	IL-1β: 0.31 pg/mL [32]
		GPS III Mini	IL-1β: 3.67 pg/mL [32]

(continued)

Table 5.1 (continued)

Growth factor or cytokine[a]	Role(s) in wound healing, musculoskeletal repair, and regeneration[a]	Reported concentrations in PRP	
		PRP system[b]	Concentration
PDGF-AB	Chemotaxis of inflammatory cells; angiogenesis; fibroblast chemotaxis and proliferation; ECM synthesis; MSC and osteoblast mitogenesis [33–35]	Arthrex	16.6681 ± 5.5123 ng/mL [23] 6.4 ng/mL [32]
		Cascade	9.7 ± 3.6 ng/mL [36]
		GPS III	42.2739 ± 2.9024 ng/mL [23] 18.7 ± 12.8 ng/mL [36]
		GPS III Mini	22 ng/mL [32]
		Harvest	133 ± 29.2 ng/mL [37]
		Magellan	34.4 ± 10.7 ng/mL [36]
		MCS 3p	117 ± 63 ng/mL [30]
		PCCS	103 ± 27 ng/mL [37]
PDGF-BB		AGF	250 ± 80 pg/mL [29]
		Cascade	14.8 ± 2.5 ng/mL [36]
		CS	204 ± 53 pg/mL [29]
		Fibrinet	3.6 ± 2.4 ng/mL [21]
		GPS	17 ± 8 ng/mL [22] 191 ± 36 pg/mL [29]
		GPS III	23.1 ± 10.1 ng/mL [36]
		Magellan	33.0 ± 8.2 ng/mL [36]
		MCS 3p	10 ± 8 ng/mL [30]
		Plateltex	14.3 ± 11.3 ng/mL [21]
		Regen	2.3 ± 1.9 ng/mL [21]
MMPs	ECM remodeling and tissue degradation [38]	Arthrex	MMP-9: 40 ng/mL [32]
		GPS III Mini	MMP-9: 222 ng/mL [32]
TGF-β1	Fibroblast activation and proliferation; ECM synthesis; endothelial chemotaxis and angiogenesis; MSC proliferation; chondrogenic and osteogenic differentiation [33, 39–41]	Arthrex	66,246.2 ± 7620.4 pg/mL [23] 20 ng/mL [32]
		Cascade	0.1 ± 0.08 ng/mL [36]
		Fibrinet	8.8 ± 5.0 ng/mL [21]
		GPS	120 ± 42 ng/mL [22]
		GPS III	141.2869 ± 12.5761 ng/mL [23] 0.1 ± 0.08 ng/mL [36]
		GPS III Mini	89 ng/mL [32]
		Magellan	0.2 ± 0.1 ng/mL [36]
		MCS 3p	169 ± 84 ng/mL [30]
		Plateltex	40.4 ± 14.9 ng/mL [21]
		Regen	6.2 ± 4.0 ng/mL [21]

Table 5.1 (continued)

Growth factor or cytokine[a]	Role(s) in wound healing, musculoskeletal repair, and regeneration[a]	Reported concentrations in PRP	
		PRP system[b]	Concentration
TGF-β2	MSC proliferation; chondrogenic and osteogenic differentiation [39–41]	MCS 3p	0.4 ± 0.3 ng/mL [30]
VEGF	Angiogenesis and vasculogenesis; macrophage and granulocyte chemotaxis [42]	Arthrex	138.7 ± 11.2 pg/mL [23]
		Cascade	0.3 ± 0.3 ng/mL [36]
		Fibrinet	0.3 ± 0.3 ng/mL [21]
		GPS	955 ± 1030 pg/mL [22]
		GPS III	142.9 ± 12.5 pg/mL [23] 2.4 ± 1.1 ng/mL [36]
		Magellan	1.2 ± 0.8 ng/mL [36]
		Plateltex	0.7 ± 0.4 ng/mL [21]
		Regen	0.1 ± 0.1 ng/mL [21]

Modified from LaPrade et al. [14]

[a]*Ang-2* angiopoietin-2, *ECM* extracellular matrix, *EGF* epidermal growth factor, *bFGF* basic fibroblast growth factor, *HGF* hepatocyte growth factor, *IGF* insulin-like growth factor, *IL* interleukin, *MMP* matrix metalloproteinase, *MSC* mesenchymal stem cell, *PDGF* platelet-derived growth factor, *TGF* transforming growth factor, *VEGF* vascular endothelial growth factor

[b]AGF: Autologous Growth Factor Filter (Interpore Cross International, LLC, Irvine, CA, USA); Arteriocyte: Arteriocyte Magellan (Arteriocyte Medical Systems, Inc., Cleveland, OH, USA); Arthrex: Arthrex ACP (Autologous Conditioned Plasma) Double Syringe System (Arthrex Inc., Naples, FL, USA); CS: Electa Cell Separator (Sorin Group Italia S.r.l, Mirandola, IT); Fibrinet: Fibrinet (Cascade Medical Enterprises, LLC, Wayne, NJ, USA); GPS: Biomet Gravitational Platelet Separation (GPS) System (Biomet Inc., Warsaw, IN, USA); GPS III: Biomet GPS III (Biomet Inc.); GPS III Mini: Biomet GPS III Mini Platelet Concentrate Separation Kit (Biomet Inc.); Harvest: Harvest SmartPReP (Harvest Technologies Corporation, Plymouth, MA, USA); MCS 3p: Haemonetics Gradient Density Cell Separator (Haemonetics Corporation, München, DE); MTF: MTF Cascade PRP System (MTF Biologics, Edison, NJ, USA); PCCS: Platelet Concentrate Collection System (Implant Innovations Inc., West Palm Beach, FL, USA); Plateltex: Plateltex (Plateltex S.R.O., Bratislava, SK); Regen: RegenPRP-Kit (RegenLab SA, Mollens, CH)

PRP therapy allows for supraphysiological concentrations of these molecules to be delivered to a site of injury to optimize, accelerate, or reinitiate tissue healing, regeneration, and repair [43, 44]. Platelet activation leads to immediate secretion of growth factors, upward of 70% in the first 10 min, and over 95% of the growth factors within 1 h [1, 37]. However, an in vitro study of PRP activated by contact with collagenous tissue, explants did not demonstrate a decrease in TGF-β1 and PDGF-BB levels between 24 and 96 h (4 days) of culture [45], suggesting that platelets may continue to synthesize and secrete growth factors after initial activation. In the absence of activation, PDGF-AB release from PRP prepared by four different systems occurred steadily out to 120 h of in vitro storage at physiological temperature (37 °C) [46].

Applications of PRP leverage the function of platelets for remodeling, repair, and regeneration. Current musculoskeletal applications of PRP include treatment

of tendinopathy, osteoarthritis, ligament and meniscus injury, muscle injury, and spine disorders. Although PRP has been promoted and publicized as a regenerative therapy, it is important to note that studies thus far have not demonstrated de facto tissue regeneration in clinical sports and spine applications.

Creation and Classification of PRP

The different forms and methods of preparing PRP are numerous, and its nomenclature reflects this variation. Platelet concentrate, platelet gel, platelet-rich fibrin matrix, platelet-rich in growth factors, and platelet-rich fibrin are names of products produced by various devices.

Protocols for deriving PRP involve a one- or more commonly two-step centrifugation procedure, which vary by time and speed. The first centrifugation step separates whole blood into platelet and cell fractions. The second centrifugation step, which is typically at higher speed, further refines the platelet fraction. The final volume of PRP produced from whole blood varies but is usually approximately 10% of the initial blood volume.

Preparation methods vary by platelet concentration, leukocyte concentration (leukocyte-rich versus leukocyte-poor), platelet activation, and use of anticoagulant. Platelet concentrations range from 2.5- to 8-fold compared to whole blood. Autologous conditioned plasma is a subclassification of PRP, which typically contains a lower fold increase in platelet concentration. Leukocyte concentration varies between leukocyte-rich (LR-PRP) and leukocyte-poor (LP-PRP) preparations. Tailoring PRP preparations to the treatment of specific clinical conditions is beginning to be evaluated more rigorously, with early data suggesting that LR-PRP is more effective for tendinopathy, while LP-PRP is superior for OA [47, 48].

Platelet activation serves as the first step in the inflammatory cascade. In the body, platelets are activated by agents such as thrombin, collagen, ADP, serotonin, and thromboxane A2. If desired during PRP preparation, exogenous platelet activation is typically achieved by the use of thrombin or calcium chloride. However, there remains no consensus on timing of activation, if exogenous activation is necessary at all prior to injection, or if activation should occur after injection, through interactions with collagen matrix in the native local environment. Due to the risk of life-threatening coagulopathy associated with bovine thrombin, secondary to antibodies to Factors V and XI and thrombin, recombinant human thrombin is available as an activation agent [49].

Finally, anticoagulants such as anticoagulant citrate dextrose-A (ACDA) or citrate phosphate dextrose are used to prevent blood clotting during PRP preparation.

More than 25 PRP preparation kits are currently available on the market [50]. A list summarizing representative kits, their underlying technology, and characteristics of the resulting PRP products is shown in Table 5.2. PRP systems can be categorized as plasma- or buffy coat-based. Plasma-based systems exclude leukocytes at

Table 5.2 Preparation of PRP by select devices and characteristics of their PRP products [51–55]

Technology	PRP system[a]	Centrifuge protocol		Activation[b]	Initial blood volume (mL)	Final PRP volume (mL)	Platelet concentration from baseline	WBC content[b]	RBC content
		Time (min)	Spins						
Plasma-based	Arthrex ACP	5	1	None	16	4–7	2–3×	LP	Poor
	MTF Cascade	6	1	$CaCl_2$	9	4.5	1.3–1.7×	LP	Poor
Buffy coat-based	Biomet GPS III	12–15	1	AT and $CaCl_2$	30 or 60	3 or 6	2–8×	LR	Rich
	Harvest Smart PReP 2	12–15	2	BT or $CaC1_2$	20 or 60	3 or 7–10	3–7×	LR	Rich
	Arteriocyte Magellan	14–20	2	$CaC1_2$	30 or 60	3–10	3–7×	LR	Rich

[a]Arteriocyte Magellan: Magellan Autologous Platelet Separator System (Arteriocyte Medical Systems, Inc., Cleveland, OH, USA); Arthrex ACP: Arthrex ACP (Autologous Conditioned Plasma) Double Syringe System (Arthrex Inc., Naples, FL, USA); Biomet GPS III: Biomet GPS III (Gravitational Platelet Separation) System (Biomet Inc., Warsaw, IN, USA); Harvest Smart PReP 2: Harvest Smart PReP 2 (Harvest Technologies Corporation, Plymouth, MA, USA); MTF Cascade: Cascade PRP System (MTF Biologics, Edison, NJ, USA)

[b]*AT* autologous thrombin, *BT* bovine thrombin, *$CaCl_2$* calcium chloride, *LP* leukocyte-poor, *LR* leukocyte-rich

the expense of some platelets, whereas buffy coat-based systems maximize platelet yield but also retain leukocytes and red blood cells (RBCs) [51].

There remains no universal classification for PRP. In 2009, Dohan Ehrenfest et al. published the first PRP classification system, based on the presence of leukocytes and fibrin architecture: leukocyte-poor or pure PRP/low-density fibrin network after activation (P-PRP), leukocyte-rich PRP/low-density fibrin network after activation (L-PRP), leukocyte-poor PRP/high-density fibrin network after activation (P-PRF), and leukocyte-rich PRP/high-density fibrin network after activation (L-PRF) [56].

In 2012, Mishra et al. added two additional classification components of platelet activation or non-activation and level of platelet enrichment [57], while Delong et al. proposed the PAW classification (P = absolute number of platelets, A = manner of platelet activation, W = presence or absence of leukocytes) [51]. The PLRA classification proposed in 2015 encompasses platelet count (P), leukocyte content (L), RBC content (R), and activation (A) [58]. The DEPA classification published by Magalon et al. encompasses four components: dose of injected platelets (D), efficiency of production (E), purity of PRP produced (P), and activation process (A) [59]. Finally, the MARSPILL classification was published in 2017, which comprises method (M; handmade or machine), activation (A; activated or not activated), red blood cells (R; rich or poor), spin (S; one or two spins), platelet number (P; folds basal), image guided (I; guided or not guided), leukocyte concentration (L; rich or poor), and light activation (L; activated or not activated) [60].

The optimal degree of fold change in platelet concentration has been debated. Early studies suggested that ideal platelet concentrations were only two- to threefold over baseline and that higher fold changes inhibited healing. These findings are in line with in vitro studies of platelet-rich plasma, where a dose-response relationship between growth factor concentrations and cell activity existed until an asymptotic level was reached, with some growth factors exerting an inhibitory effect at sufficiently high concentrations [61]. This has been clarified by follow-up studies, which suggested that fold changes in the range of five- to sevenfold were ideal and that inhibition did not occur until up to tenfold increase over baseline [62].

Buffy coat-based PRP systems that produce higher platelet concentrations tend to produce higher leukocyte and RBC concentrations as well [51]. The controversy over leukocyte concentration has revolved around neutrophils and their association with pro-inflammatory cytokines, interleukin 1 (IL-1) and tumor necrosis factor (TNF-α), which may exacerbate inflammation in osteoarthritis or acute muscle injuries. LR-PRP has been shown to cause synoviocyte cell death in culture and increase expression of inflammatory markers [47]. Likewise, the presence of RBCs in PRP is controversial, as RBCs have been documented to cause chondrocyte death [47, 63]. However, the leukocytes in PRP also contain monocytes, which differentiate into macrophages. While the primary function of macrophages was previously thought to be only for phagocytosis, it is now recognized that different types of activated macrophages exist, which have pro-inflammatory (M1) and anti-inflammatory (M2) roles. The M2 macrophage has specific functions in wound healing, which may assist tissue repair. A PRP formulation enriched with M2 macrophages may therefore be ideal for certain tissue pathologies. Newer PRP devices are able to achieve higher platelet concentrations while minimizing both WBC and RBC content through a two-spin suspension protocol.

Differences in PRP composition are related not only to variation in preparation methods but also to variation among patients, given the autologous nature of PRP. Both age and sex are known to influence PRP composition. A study of 39 healthy patients with no history of orthopedic problems and no current NSAID, antiplatelet, or aspirin use reported significant differences in composition of LP-PRP from male versus female subjects, with sex influencing growth factor and cytokine profile more than age [64]. In this study, substantial variability in PRP composition was found within groups of male and female subjects stratified by age (“young” group aged 18–30 years, “older” group aged 45–60 years). Nevertheless, PRP from male patients consistently contained significantly higher levels of growth factors and cytokines than PRP from female patients (TGF-β1, basic fibroblast growth factor, IL-1β, interleukin 1 receptor antagonist protein, TNF-α). Variation due to age was detected only in significantly lower IGF-1 levels in PRP from “older” versus “young” patients. Extrapolation of this data from healthy subjects to patients with musculoskeletal or spine disorders is difficult, as the latter group may have various medical co-morbidities or take medications that were excluded from this study. However, donor factors such as age and gender, and processing factors such as the

time of day of platelet collection [65] are variables that are recognized to influence the growth factor and cytokine composition of PRP, in addition to other variables in PRP preparation previously discussed in this section.

Clinical Applications of PRP

Over 400 clinical trials of PRP are listed on ClinicalTrials.gov for various diseases and conditions [66]. In this section, we discuss clinical applications of PRP and the current level of evidence supporting its use for musculoskeletal and spine disorders.

Tendinopathy

Tendon injuries are common in both active and more sedentary people and may occur acutely or secondary to overuse [67]. Acute injuries are classified as tendinitis during the active, acute inflammation phase and tendinosis during the chronic, non-healing phase, characterized by a lack of inflammatory cells on histology in addition to evidence of aberrant tissue repair and thickening, collagen degeneration, and neovascularization [68]. Tendinopathy is a general term for tendon disorders, and chronic tendinopathy for conditions that remain refractory to conventional treatment. Sustained or repetitive injury over time may lead to chronic pathology, disability, and loss of function. Chronic tendinopathy is postulated to be a quiescent state along the spectrum of tendon pathology, an abnormal healing response or stage of stasis, in contrast to the inflammation and inflammatory cell infiltration present in early tendinopathy [69].

In this setting, the goal of biologic agents in the treatment of chronic tendinopathy is to restore or restart the healing process within the local tissue environment, rather than decreasing inflammation in more acute or subacute injuries. In laboratory and preclinical studies, PRP enhanced ECM synthesis of tenocytes and tendon explants in vitro [45, 70, 71] and promoted patellar tendon repair in a rat model [72].

Applications of PRP for chronic tendinopathy has been investigated in multiple clinical studies. The most current evidence from a systematic review and meta-analysis of 18 randomized controlled trials (RCTs) of PRP for treatment of tendinopathy supported the use of a single injection of LR-PRP using a peppering technique intratendinously under ultrasound guidance [48]. Here we discuss specific findings of PRP for lateral epicondylar (common extensor), patellar, and Achilles tendinopathy, although the clinical use of PRP applies to rotator cuff, gluteus medius, hamstring, and other sites of tendinopathy as well.

A RCT of 100 patients with chronic lateral epicondylar tendinopathy compared PRP with corticosteroid injection, which demonstrated a significant improvement in pain and function after follow-up out to 2 years [73, 74]. Krogh et al. recruited

60 patients with chronic lateral epicondylar tendinopathy for a RCT comparing treatment by PRP, saline, or glucocorticoid injections and found no difference in pain reduction at their primary end point of 3 months [75]. A double-blind RCT of 230 patients with chronic lateral epicondylar tendinopathy, treated by dry needling with or without leukocyte-rich PRP, yielded significant improvement in elbow tenderness and pain at 24 weeks post-intervention for the PRP treatment group [76]. Most recently, a systematic review of RCTs compared clinical outcomes of PRP, autologous blood, and corticosteroid injections for lateral epicondylar tendinopathy [77]. A network meta-analysis of 10 eligible studies out of 374 identified RCTs concluded that both PRP and autologous blood injections improved pain compared to corticosteroid, but autologous blood injections had a higher risk of complications than PRP.

LR-PRP treatment for patellar tendinopathy was studied in a double-blind RCT of 23 patients and was compared to dry needling alone [78]. Both groups underwent a standardized eccentric exercise program in addition to the intervention. Subjects that received PRP demonstrated greater clinical improvement at 12 weeks post-intervention, but this early improvement did not persist, as no significant difference was found between groups after 26 weeks. In contrast, in a RCT of 46 athletes with patellar tendinopathy, where subjects were randomized to two PRP injections over 2 weeks or 3 sessions of focused extracorporeal shockwave therapy, subjects who received PRP injections demonstrated improved pain and function at later time points of 6- and 12-month follow-up [79]. The most recent evidence from a systematic review and meta-analysis of studies of nonoperative management for patellar tendinopathy (PRP, extracorporeal shockwave therapy, eccentric exercise) suggests that multiple PRP injections ($\geq$2) offer more satisfactory results in terms of pain and function at follow-up $\geq$6 months [80].

However, there was no difference in pain or activity level out to 24 weeks in a double-blind RCT of 54 patients with chronic Achilles tendinopathy randomized to PRP or a saline placebo treatment, followed by an eccentric exercise program [81]. More recently, a RCT of 24 patients with chronic Achilles tendinopathy treated with PRP or saline injections did not report any improvement in pain or function at 3 months, and the study itself was limited by large dropout rate [82]. Overall, the most recent data suggest that PRP is less effective for Achilles tendinopathy than other sites. Two separate meta-analyses of PRP versus placebo (saline) injection [83] and of autologous blood-derived products [84] including PRP compared to placebo (sham injection, no injection, or PT alone) reported that PRP injections were not more effective than placebo for Achilles tendinopathy.

Table 5.3 summarizes the results of selected clinical trials of PRP for chronic tendinopathy. Although the findings are promising and generally supportive of PRP for treatment of chronic tendinopathy, inconsistencies and variation in outcomes from these studies reflect variation in PRP preparation methods, choice of control intervention, post-intervention rehabilitation protocols, and anatomic sites of pathology.

Table 5.3 Select clinical trials of PRP for lateral epicondylar, patellar, and Achilles tendinopathy (Level I evidence only)

Site of tendinopathy	Study purpose[a]	Year of publication	Sample size	Follow-up	PRP system and reported composition[b]	Injection technique	Post-procedure rehabilitation protocol[a]	Conclusions
Lateral epicondylar	LR-PRP vs. CS injections [73, 74]	2010, 2011	100 PRP: 51 CS: 49	1 [73] and 2 years [74]	Biomet Recover 3 mL LR-PRP No activation	Needling	24 h–2 weeks: Standardized stretching protocol under PT supervision 2–4 weeks: Formal eccentric muscle- and tendon-strengthening 4 weeks: Return to activity as tolerated	PRP significantly reduces pain and increases function out to 2-year follow-up
	PRP vs. CS vs. saline injections [75]	2013	60 PRP: 20 CS: 20	3 months	Biomet Recover GPS II 3–3.5 mL PRP 8× platelets	Needling Ultrasound guidance	3–4 days: Standard tennis elbow stretching and training program prescribed	No difference among PRP, CS, and saline in pain reduction at 3 months
Patellar	2 PRP injections over 2 weeks vs. 3 ESWT sessions at 48–72-h intervals [79]	2013	46 PRP: 23 ESWT: 23	12 months	MyCells 2 mL PRP 0.89–1.1 × 10^9 platelets/mL 3–5× platelets No activation	PRP injections with needling Ultrasound guidance	1–2 weeks: Standardized stretching and strengthening protocol 2 weeks: Water activities as tolerated 4 weeks: Return to previous training activity as tolerated	PRP injections lead to significant improvement in symptoms and pain at 12-month follow-up

(continued)

Table 5.3 (continued)

Site of tendinopathy	Study purpose[a]	Year of publication	Sample size	Follow-up	PRP system and reported composition[b]	Injection technique	Post-procedure rehabilitation protocol[a]	Conclusions
	LR-PRP with needling vs. dry needling [78]	2014	23 PRP: 10 Dry needling: 13	≥26 weeks	Biomet GPS III 6 mL LR-PRP	Needling Ultrasound guidance	5-phase program of eccentric exercises, supervised by PT Patients assessed by PT to determine appropriate starting phase	Ultrasound-guided LR-PRP injections with needling and standardized eccentric exercise accelerated early recovery and symptom improvement at 12 weeks, but the apparent benefit of PRP dissipated by ≥26 weeks
Achilles	PRP vs. saline injections [85, 86]	2010, 2011	54 PRP: 27 Saline: 27	24 [85] and 52 [86] weeks	Biomet Recover 4 mL PRP No activation	Needling Ultrasound guidance	First 48 h: Walk short distances indoors Day 3–7: Up to 30 min walks 1–2 weeks: Stretching exercises 2–14 weeks: Daily eccentric exercise program 4 weeks: Gradual return to sports activities	No difference between PRP and saline injections in pain and activity level at 24- or 52-week follow-up

	PRP vs. saline injections [82]	2016	24 PRP: 12 Saline: 12	3 months	Biomet Recover GPS II 6 mL PRP 8× platelets	Needling	First 4 days: Minimize strain	PRP injections did not improve pain and function at 3-month follow-up
						Ultrasound guidance	Day 5: Home therapy rehabilitation protocol including strengthening, eccentric training, stretching, coordination	

[a]*$CaCl_2$* calcium chloride, *CS* corticosteroid, *LR-PRP* leukocyte-rich PRP, *PT* physical therapy

[b]Biomet GPS III: Biomet GPS III (Gravitational Platelet Separation) System (Biomet Inc., Warsaw, IN, USA); Biomet Recover GPS II: Recover GPS II (Gravitational Platelet Separation) System (Biomet Inc.); Biomet Recover: Recover Platelet Separation Kit (Biomet Inc.); MyCells: MyCells Autologous Platelet Preparation System (Kaylight Ltd., Ramat-Hasharon, IL)

Osteoarthritis

Osteoarthritis (OA) is a leading cause of pain and disability in adults and is multifactorial in etiology. However, to date, there remain no disease-modifying therapies for OA that can reverse or prevent the structural changes found in later stages of disease. Laboratory studies have observed that PRP enhances chondrogenic differentiation of mesenchymal stem cells, proliferation, and ECM synthesis, leading to multiple clinical trials to assess the utility of PRP for treatment of OA, most notably of the knee and hip [87].

A systematic review of PRP injections for knee OA yielded three meta-analyses that met criteria, which compared outcomes of intra-articular PRP versus control hyaluronic acid or placebo injections [88]. Campbell et al. reported that PRP treatment led to clinically relevant improvements in symptom relief and function as early as 2 months, peaking at 6 months, and persisting up to 12 months post-intervention. They note variation in protocol, including number (1–4) of and timing (1–3 weeks) between PRP injections, PRP volume injected, one- versus two-step centrifugation, and platelet activation, as well as variation in patient profile including age, duration of pain, and severity of OA. Their findings also suggested that PRP is more effective for patients with only evidence of early radiographic evidence of OA or lower Kellgren-Lawrence grade. They were unable to determine if multiple PRP injections were helpful, although multiple injections may increase the risk of local adverse reactions. The variability across the three meta-analyses precluded conclusions regarding other protocol parameters. They did conclude that higher-quality RCTs were necessary to persuade insurance providers to provide coverage for PRP for knee OA. Most recently, a meta-analysis of RCTs reported that intra-articular PRP injection provides more pain relief and functional improvement in patients with symptomatic knee OA at 1-year follow-up compared to HA and saline [89].

While OA is traditionally described as a non-inflammatory arthritis, characterized by cartilage degeneration, it is now understood that OA affects all tissues within the joint and that inflammation plays a central role in both the onset and progression of disease. There has been much speculation that the role of PRP for clinical treatment of OA lies more in its anti-inflammatory and immunomodulatory effects for pain rather than its regenerative properties [52, 90]. In vitro studies have demonstrated that growth factors present in PRP can function in an anti-inflammatory role via the lipoxin LXA_4 [9], which acts to resolve inflammatory processes, and that PRP modulates IL-1 production by macrophages [91].

Therefore, LP-PRP has been the preferred formulation for treatment of OA, given the concern for pro-inflammatory effects of neutrophils in LR-PRP preparations. Laboratory studies have demonstrated that LP-PRP decreased catabolism and increased tissue synthesis by chondrocytes [92]. A correlation was found between increasing leukocyte concentration and elevated inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-8) [93]. Synoviocytes exhibited significant cell death and pro-inflammatory response with LR-PRP treatment, further supporting recommendations of LP-PRP preparations for intra-articular applications [47].

To this end, a meta-analysis of 6 RCTs and 3 prospective studies, totaling 1055 patients, compared outcomes and adverse effects of LP- and LR-PRP against control hyaluronic acid (HA) or placebo injections for knee OA [94]. Riboh et al. detected a small improvement in functional outcome scores in favor of LP-PRP versus LR-PRP compared with HA and placebo and did not detect any significant difference in safety profile between the two PRP formulations. Both LR- and LP-PRP were associated with a higher incidence of transient reactions such as local swelling and pain compared to HA. They again noted low-quality evidence due to variation in PRP preparation methods, even among LP- and LR-PRP formulations, and variation in severity of OA between treatment groups. Moreover, the analyzed studies skewed toward younger patients with milder OA.

Few studies have been published of PRP for hip OA, and two level I studies did not demonstrate long-term benefits of PRP versus HA at 1 year [95, 96]. A meta-analysis reported that patients with hip OA treated with PRP had improvements in pain and function at 2 months, but these changes were not sustainable, as there was no difference versus HA control at 6 and 12 months [97].

Table 5.4 lists the findings of selected clinical trials of PRP for OA. Overall, for knee OA, evidence suggests that LP-PRP improves pain and provides symptom relief for upward of 1 year following intervention. Selection of candidates with earlier stages of knee OA may prove more efficacious. In contrast, studies have not demonstrated a benefit of PRP over HA in treatment of symptomatic hip OA.

Ligament and Meniscus Injuries

PRP has been studied for treatment of ligament injuries, primarily in the context of enhancing surgical outcomes of anterior cruciate ligament (ACL) reconstruction, which is outside the scope of the nonoperative applications discussed in this chapter. In vitro studies have shown that PRP enhanced ACL cell viability and collagen production [104]. Overall, there is promising evidence that PRP can improve outcomes for ACL reconstruction [105, 106]. In addition, the ongoing Bridge-Enhanced ACL Repair (BEAR) Trial led by Murray et al. is investigating biologic augmentation of surgical ACL repair by PRP [107, 108].

Scant literature exists on the nonoperative treatment of ligament injuries by PRP. Laboratory studies have demonstrated that PRP stimulated DNA and collagen synthesis in human periodontal ligament cells [109, 110], and increased gene expression and synthesis of ECM proteins in equine suspensory ligament cells [45, 111]. Preclinical animal studies have utilized PRP to augment healing of medial collateral ligament (MCL) ruptures in a rabbit model and demonstrated greater mechanical strength of MCLs treated with PRP [112].

Case reports and series have been published for partial tears of the ulnar collateral ligament of the elbow in throwing athletes, suggesting a shorter return to play (RTP) following treatment with PRP [113, 114]. A small RCT of sixteen elite athletes with high ankle sprains (anterior inferior tibiofibular ligament tears) and

Table 5.4 Select clinical trials of PRP for osteoarthritis (OA) of the knee and hip (Level I evidence only)

Site of OA	Study purpose[a]	Year of publication	Sample size	Kellgren-Lawrence grade	Follow-up	PRP system and reported composition[b]	Injection technique	Conclusions
Knee	Series of 3 weekly injections: PRP vs. HA [98, 99]	2015, 2019	192 PRP: 96 HA: 96	0–3	12 months [98], 24 months [99]	Hematology protocol with two spins 5 mL PRP 1.1 ± 0.5× WBCs 4.6 ± 1.4× platelets $CaCl_2$ activation	Intra-articular	Both PRP and HA were effective in improving symptoms and function over 24-month follow-up with no significant differences
	Series of 3 weekly injections: LP-PRP vs. saline [100]	2016	30 LP-PRP: 15 Saline: 15	2–3	1 year	Arthrex ACP 4–7.1 mL LP-PRP	Lateral parapatellar approach	LP-PRP provides pain relief and functional improvement out to 1-year follow-up
	Series of 3 weekly injections: LP-PRP vs. HA [101]	2017	99 PRP: 49 HA: 50	1–4	1 year	Arthrex ACP 4 mL LP-PRP 790 ± 0.11 WBCs/mL 1.73 ± 0.05× platelets	Intra-articular Ultrasound guidance	No difference between PRP and HA in pain, but significant improvement in function for PRP, out to 1-year follow-up
	2 PRP 1 month apart vs. 1 HA vs. 4 ozone gas injections in 1 week [102]	2017	102 patients PRP: 41 HA: 40 Ozone: 39	2–3	12 months	Ycellbio 5 mL PRP 9–13× platelets $\geq 1.5 \times 10^6/\mu L$ platelets No RBCs No activation	Intra-articular	PRP was superior to HA and ozone injections for improvement in pain and function out to 12-month follow-up

	Series of 3 weekly injections: 3 PRP vs. 1 PRP and 2 saline vs. 3 HA vs. 3 saline [103]	2017	162 patients 3 PRP: 46 1 PRP: 45 3 HA: 46 Saline: 45	Early (1–3) vs. advanced (4)	6 months	Hematology protocol with 2 spins 5 mL PRP 5.2–5.3× platelets 1.1–1.2 × 10^6/μL platelets $CaCl_2$ activation	Superolateral approach	Multiple (3) PRP injections achieve better clinical results for early OA, but no difference among injections in patients with advanced OA
Hip	Series of 3 biweekly injections: PRP vs. HA [96]	2013	100	2–4	12 months	Hematology protocol with 2 spins 5 mL PRP 6× platelets 6–8 × 10^6/mL platelets 8300 WBCs/μL No RBCs $CaCl_2$ activation	Ultrasound guidance	Pain and function improvement detected in both groups with no significant differences between PRP and HA out to 12-month follow-up
	Series of 3 weekly injections: LP-PRP vs. HA [95]	2016	43 PRP: 21 HA: 22	2–3	16 weeks	Regen 3 mL LP-PRP 1–1.5× platelets	Ultrasound guidance	PRP provided immediate improvement in pain that was not maintained at 16-week follow-up

[a] *$CaCl_2$* calcium chloride, *HA* hyaluronic acid, *LP-PRP* leukocyte-poor PRP

[b] Arthrex ACP (Autologous Conditioned Plasma) Double Syringe System (Arthrex Inc., Naples, FL, USA); Regen: RegenPRP-Kit (RegenLab SA, Mollens, CH)

dynamic syndesmosis instability randomized patients to receive ultrasound-guided PRP injections with rehabilitation versus rehabilitation only [115]. Subjects from both groups followed an identical rehabilitation protocol. In this small study, the PRP group demonstrated shorter RTP, syndesmosis re-stabilization, and decreased residual pain over time. However, further studies with higher levels of evidence are necessary to support the use of PRP for ligament injuries.

PRP has also been studied as a means to augment healing of meniscal tears in the avascular zone, which intrinsically do not heal and are typically surgically resected. Over time, loss of even a portion of the meniscus through arthroscopic partial meniscectomy predisposes to development of post-traumatic OA. To this end, preclinical and clinical studies have investigated the utility of PRP for meniscal repair and regeneration and for augmentation of surgical repair outcomes. In vitro, PRP increased rabbit meniscal cell proliferation and ECM synthesis compared to platelet-poor plasma (PRP) [116]. In vivo, PRP combined with gelatin hydrogel was implanted into meniscal defects in the avascular zone using a rabbit model. Compared to hydrogel without PRP, defects treated with PRP demonstrated greater cell numbers and ECM production, suggesting PRP can enhance the healing potential of the avascular zone of the meniscus.

In a case-control study of 34 patients undergoing open meniscal repair, the group that received PRP to augment repair demonstrated slight improvement at 1 year post-operatively [117]. In a separate study of surgeons performing 35 arthroscopic meniscus repairs with or without PRP augmentation, the addition of PRP was not found to influence reoperation rate [118]. To date, there have not been studies with higher levels of evidence published on the efficacy of PRP to guide nonoperative management of meniscal tears of traumatic or degenerative etiologies, although PRP is utilized for these applications in clinical practice. Therapeutic effects observed from PRP for degenerative meniscal tears in the setting of associated OA may result indirectly from treatment of the OA rather than the meniscal pathology itself.

Muscle Injuries

There is scant literature published on the use of PRP for muscle injuries. Hammond et al. completed a laboratory study using a rat model of an acute tibialis anterior muscle strain injury, treated with PRP, PPP, or no injection [119]. They demonstrated that PRP decreased recovery time in a small animal model and postulated that this was secondary to induction of myogenesis by growth factors present in PRP. A statistically significant decrease in recovery time was also reported in a RCT of 28 patients with acute hamstring injuries who were allocated to PRP with rehabilitation (26.7 ± 7.0 days) versus rehabilitation alone (42.5 ± 20.6 days), although there was substantial variance in the results [120]. In a double-blind, placebo-controlled RCT of 80 athletes with acute hamstring injuries, subjects were allocated to PRP or placebo saline injections, but did not demonstrate benefit of PRP in return to play or reinjury rate [121]. The most current meta-analysis of PRP for acute muscle injuries concluded with limited evidence that PRP may allow earlier return to play

for patients with acute grade I or II muscle strains without a significant increase in risk of reinjury out to 6 months of follow-up [122].

Follow-up laboratory studies have suggested that depletion of platelets is more favorable for myocytes. Mazzocca et al. reported that a one-spin PRP protocol yielding lower platelet concentration increased myocyte proliferation [123]. Miroshnychenko et al. studied the effects of various PRP formulations on in vitro myogenic differentiation [124], and found that LR-PRP led to myoblast proliferation, but PPP and LR-PRP subjected to a second spin to remove platelets induced myoblast differentiation. It is clear that further clinical studies with higher levels of evidence must be performed, and may require consideration of tailoring PRP formulations specifically for treatment of muscle injuries.

Spine Disorders

Low back pain is among the most common outpatient complaints. Consequently, there is particular interest in PRP for treatment of disorders associated with low back pain, such as intervertebral disc (IVD) degeneration and facet joint osteoarthritis. In vitro laboratory studies have demonstrated that PRP stimulates proliferation and matrix synthesis by cells from both the nucleus pulposus (NP) and annulus fibrosus (AF) [125, 126]. PRP has also been shown to exhibit anti-inflammatory effects on NP cells exposed to pro-inflammatory cues [127]. A preclinical study utilized a rabbit model of IVD degeneration [128], injecting PRP in gelatin hydrogel microspheres into the NP, and comparing outcomes to control saline and sham groups. At 8 weeks, the authors noted suppression of degeneration with histologic evidence of ECM synthesis in animals injected with PRP. A follow-up study demonstrated greater IVD height on MRI and decreased apoptosis in the NP after PRP injection [129]. These findings were further verified in another rabbit study of IVD degeneration, comparing intradiscal PRP versus PPP injections [130].

In this setting, a few clinical studies of intradiscal PRP injections for low back pain have been performed with early but promising results. A prospective study of 22 patients who underwent intradiscal PRP injections (single-level to as many as five levels) demonstrated early improvement in pain and function out to 6 months [131]. A prospective, double-blind RCT of 47 patients with chronic discogenic low back pain received intradiscal PRP or contrast agent [132]. The 29 patients who received intradiscal PRP injections reported significant improvement in pain and function at 8 weeks through at least 2 years of follow-up [133].

Analogous to studies of PRP for OA at other anatomic sites, two studies on intra-articular PRP injections for lumbar facet joint syndrome were published by the same group of investigators. The first is a prospective study of 19 patients who received PRP injections, which demonstrated significant improvement in pain and function within a short-term study period of 3 months [134]. This group of investigators led by Wu et al. proceeded to a prospective RCT of 46 patients with lumbar facet joint syndrome, randomized to injections of PRP versus corticosteroid with local anesthetic (LA), with up to 6 months of follow-up [135]. Subjects who

received corticosteroid/LA injections experienced initial improvement in pain and function, which decreased after 6 months. In contrast, subjects treated with PRP continued to experience improvement in pain and function out to 6 months.

For radicular pain, Centeno et al. has published the results of a case series of 470 patients who received lumbar epidural injections of platelet lysate, which consists of growth factors prepared by lysing platelets and removing cell debris [136]. Within the limitations of a case series, patients reported significant improvements in pain and function through 2 years of follow-up.

Although promising so far, more rigorous studies with higher levels of evidence must be performed to further investigate the utility of PRP for spine disorders.

Advantages of PRP

The primary advantage of PRP is the ability to offer more nonoperative treatment options for patients who have failed conventional treatment, who do not want surgery, or who are poor surgical candidates and for conditions with poor surgical outcomes, such as degenerative tendinopathies or meniscal tears.

Moreover, the autologous nature of PRP is thought to eliminate or at least minimize risk of immune rejection or disease transmission. Assuming sterility in preparation, the risk of contamination is low. Potential risks of PRP administration include adverse effects arising from the use of bovine thrombin used for platelet activation, which can rarely cause coagulopathy from antibody formation. Bovine thrombin is now avoided due to these risks, although earlier studies of PRP for non-musculoskeletal applications reported its use for platelet activation during oral and maxillofacial surgery [137–140] and wound care [29, 141–145].

Although there exists immense variation in PRP protocols, the procedure can be performed during the point of care in an office setting with access to phlebotomy services and a commercial PRP system. Although the cost of commercial PRP kits is not negligible, a standard hematology protocol for PRP preparation requires a little more than a centrifuge and basic laboratory supplies. This technology has been implemented in the global arena through the creation of a PRP injection program in Tanzania at the Bugando Medical Centre [146], via a collaboration with the local blood bank, providing proof of principle that access to PRP interventions can be achieved with minimal additional cost and resources.

Disadvantages of PRP

Disadvantages of PRP lie in the variability already well described in this chapter, including the lack of standardization in PRP preparation methods and reporting of PRP composition in literature, which limits comparisons between studies, coupled with the lack of one universally accepted classification scheme. High variability

exists among patients, including donor factors such as age, gender, and comorbidities, and even among underlying patient conditions. Although clinical trials study PRP for specific pathologic conditions and utilize rigorous criteria for patient selection, there remains considerable heterogeneity among patients diagnosed with the same condition in terms of chronicity of symptoms and prior treatments such as oral medications, rehabilitation, and other injections. The durability of any intervention for musculoskeletal and spine disorders depends upon the quality of post-intervention rehabilitation and patient adherence to a home exercise program. Post-PRP rehabilitation protocols are not standardized for various conditions, and variability in therapy plays a significant role in the long-term outcomes of PRP intervention.

The success of a PRP intervention hinges on clinically significant improvement in standardized but subjective patient-reported outcomes of pain and function. The burden of proof for clinical efficacy of an intervention is all the more difficult to achieve when one considers that intra-articular saline placebo injections for knee OA have been reported to have both a statistically and clinically significant effect on pain and function out to 6-month follow-up [147]. Therefore, clinical investigators are now quantifying cytokine levels in the synovial fluid before and after PRP intervention for knee OA, in order to correlate clinical outcomes with the biological mechanisms of action of PRP [148].

Contraindications to PRP therapy include cancer (tumor or metastatic disease), active infections, thrombocytopenia, and pregnancy [149]. Growth factors such as isoforms of TGF-β and hepatocyte growth factor, found in PRP, have been associated with tumor growth [150], hence the relative contraindication in patients with cancer history. However, PRP has been utilized for patients with avascular necrosis of the mandible in cancer patients with a history of bisphosphonate use [151–153] and non-musculoskeletal applications in patients undergoing surgical tumor or complications related to active chemotherapy treatment [154, 155].

Finally, PRP therapy is not covered by insurances for the applications described in this chapter, which can pose a significant financial burden for patients. Wide variability in cost is present, to upward of $2000 or more per injection [2], based on many factors including the cost of the specific kit used for preparation and other local economic influences. The cost of PRP therapy is related to its off-label use for musculoskeletal and spine disorders, which do not have FDA approval.

Regulation of PRP

The clinical applications of PRP for musculoskeletal and spine disorders discussed in this chapter are considered off-label. PRP is a biologic and falls under the regulation of the FDA Center for Biologics Evaluation and Research (CBER). Under the Code of Federal Regulations (CFR) Title 21, PRP and other blood products are exempt from the FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps) [156]. Instead, the 510(k) application pathway has

been used for clearance of PRP preparation systems that are considered "substantially equivalent" to other existing or predicate devices already available on the market. The first PRP preparation systems were reviewed by the Office of In Vitro Diagnostics and Radiological Health, received 510(k) clearance based upon predicate centrifuge devices, and were therefore classified as centrifuges.

The 510(k) pathway for clearance of PRP devices does not strictly require clinical data for FDA approval, as they are considered lower-risk devices and "substantially equivalent" to a previously cleared device [157]. The term "clearance" designates the limitations of use of the device, only to the indications of the predicate device that it has been determined to be "substantially equivalent." This is in contrast to other regenerative therapies, which may receive "approval" through traditional FDA regulatory pathways as new drugs via new drug applications (NDA) or biologics license applications (BLA), which further require clinical data collected via investigational new drug (IND) or investigational device exemption (IDE) applications.

As early as February 2011, CBER granted 510(k) clearance to devices for mixing PRP with bone graft to improve its handling, for application to bony defects in the operative setting ("Platelet And Plasma Separator For Bone Graft Handling") [158]. Injection or implantation of PRP without mixing with bone graft materials falls outside the intended use of these PRP systems and is considered off-label use. However, a clinician may still practice off-label use of PRP for musculoskeletal and spine disorders but may not market the use of the device for these off-label applications. CBER does not require an IND or IDE application to the FDA or institutional review board (IRB) approval for off-label use [159].

In 2007, the AutoloGel™ System (Cytomedix Inc., Gaithersburg, MD) received 510(k) clearance for topical application in the management of cutaneous wounds including chronic nonhealing diabetic, pressure, or venous wounds. Mixing PRP with bone graft for defects and topical application for chronic wounds remain the sole indications of use for PRP that have received FDA approval, although these treatments are considered experimental by insurance providers including the Centers for Medicare and Medicaid Services (CMS), with limited to no coverage at this time [160].

While PRP is not subject to FDA regulation of HCT/Ps under CFR Title 21, Part 1271, further activation of PRP by exogenous agents following centrifugation alone creates a potentially tricky situation in which PRP may be considered more than "minimally manipulated" and therefore subject to further regulation. Although no changes have yet occurred that impact off-label use of PRP, clinicians should remain up-to-date with the latest FDA regulatory stance on PRP.

Future Directions

Since its inception in the early 2000s, PRP therapy has rapidly entered the mainstream for applications as diverse as musculoskeletal and spine disorders to alopecia and aesthetics. The lack of conclusive scientific evidence of clinical efficacy, FDA

approval, and insurance coverage has not significantly hindered the popularity of PRP therapy or patient interest.

Regulatory approval and insurance coverage decisions depend upon demonstrating higher-level supportive evidence of both safety and clinical efficacy of PRP therapy. This in turn requires a decrease in the variability found in prior PRP studies, which can be achieved in part by adoption of one universally accepted PRP classification scheme, and standardization in preparation methods, characterization, and reporting of PRP composition across clinical trials. Delivery of PRP must also be standardized, such as number and timing of injections and concurrently performed interventions such as percutaneous tenotomy, as well as post-procedural care with pathology-specific rehabilitation protocols. FDA approval for additional indications of PRP therapy requires a BLA or premarket approval (PMA) application, which involves larger-scale clinical studies that should be designed with close consideration of these variables in mind.

Although clinicians and patients have found success with PRP for the musculoskeletal and spine disorders described in this chapter, there remains a limited understanding of the precise pathophysiology that underlie these diseases. Without this knowledge, it is difficult to determine the precise targets of PRP therapy for each disease process and what relevant characteristics in PRP impact clinical response in patients. While current evidence suggests that LR-PRP is more suitable for tendinopathy and LP-PRP for OA, future work must continue to probe and define the growth factors and cytokine cocktails that are ideal for specific pathologies and develop novel methods of PRP preparation that yield these customized formulations.

Efforts are already underway in recently published studies of PRP for OA [148], in which investigators are measuring cytokine levels in synovial fluid to better understand the local effects of PRP, further refine its mechanism of action, and identify and validate biomarkers of disease. Since PRP is believed to improve pain and function for patients with OA through anti-inflammatory effects, the goal will be to demonstrate that decreasing inflammation will in turn slow progression of OA and ultimately, that PRP is a disease-modifying therapy for early-stage OA.

Although PRP is considered a regenerative therapy, based largely upon the effects of growth factors on cells and tissues in laboratory studies, convincing evidence of tissue regeneration has yet to be demonstrated in clinical studies. Demonstration of tissue regeneration is limited in part because clinical study results typically report standardized patient-reported outcomes without biological correlates or biomarkers that can support the potential efficacy of the intervention. Incorporation of OA biomarkers developed and validated for pain and disease progression [161] allows for a more objective measurement of pain improvement due to PRP and potential disease-modifying properties.

In summary, PRP is a promising therapy that offers a nonsurgical approach to treatment of musculoskeletal and spine disorders, for patients who have failed conventional therapy or with conditions that have poor surgical outcomes. However, there remains much to elucidate in the basic science and underlying mechanism of action of PRP, in order to accelerate regulatory approval and insurance coverage and

expand access to PRP treatment for patients of all socioeconomic background. In the future, PRP therapy will require a personalized approach, tailoring PRP formulations for both patient-specific and condition-specific characteristics.

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