Platelet-Rich Plasma: Basic Science and Biological Effects

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ABSTRACT

PLATELET-RICH PLASMA (PRP) IS AN AUTOLOGOUS BIOLOGICAL INTERVENTION THAT SEEKS TO AUGMENT THE BODY'S SELF-HEALING CAPACITY. AS A PROMISING NONSURGICAL TREATMENT OPTION FOR MUSCULOSKELETAL INJURIES, PRP HAS ENTHUSED SIGNIFICANT INTEREST AMONG PATIENTS AND SPORTS MEDICINE PROFESSIONALS. OWING TO A GROWING RANGE OF CLINICAL INDICATIONS AND EXCELLENT SAFETY PROFILE, SPORTS MEDICINE PROFESSIONALS ARE LIKELY TO ENCOUNTER INDIVIDUALS WHO RECEIVED OR ARE CONSIDERING PRP. THIS ARTICLE PROVIDES AN OVERVIEW OF PRP, BIOLOGICAL MECHANISMS, AND EVIDENCE UNDERPINNING THE UTILIZATION OF PRP INJECTIONS FOR MUSCULOSKELETAL DISORDERS. A COMPANION ARTICLE IN THIS ISSUE DISCUSSES CONSIDERATIONS FOR SPORTS MEDICINE PROFESSIONALS MANAGING INDIVIDUALS FOLLOWING PRP PROCEDURES.

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INTRODUCTION

Regenerative medicine (RM) is an emerging interdisciplinary medical specialty that has been used for decades in dentistry and surgery (40). Owing to a growing body of literature and enthusiasm for nonsurgical healing of musculoskeletal injuries (e.g., tendinopathy and osteoarthritis [OA]), RM has gained considerable attention among the sports medicine professions. Moreover, public awareness of RM has soared from media coverage of high-profile athletes receiving treatments (43). In health care, RM is a ubiquitous term used to describe clinical applications focused on the repair, replacement, or regeneration of cells and tissues. Because these clinical applications seek to stimulate and harness the body's own healing capacity, the concept of tissue regeneration is favored over repair (24). Nevertheless, regeneration and repair coexist as part of the desired healing process, particularly regarding soft-tissue injuries.

Musculoskeletal disorders are the most common cause of long-term pain and physical disability among athletes and the general population (102). Advances in the understanding of chronic musculoskeletal conditions, coupled with the untoward risk profile of many interventions (e.g., opiates, corticosteroids, and surgery), have fueled interest in alternative treatments such as RM. The growing interest for RM resides in the need for a minimally invasive intervention with an excellent safety profile that requires minimal recovery or downtime from activity and sports.

With regard to musculoskeletal disorders, autologous RM applications include but are not limited to stem cell preparations and platelet rich plasma (PRP). Of these applications, PRP is the most commonly performed and least invasive procedure. In 2015, 160 million U.S. dollars were reportedly spent (payment to providers) on PRP with an anticipated increase to 451 million expected by 2024, with musculoskeletal injuries occupying the largest share of these costs (98). Musculoskeletal indications for PRP applications include, but are not limited to, OA and soft-tissue injuries such as tendinopathy and ligament sprains. In addition, PRP may be used as a means of augmenting surgical repair (e.g., PRP used in a fibrin scaffold during rotator cuff repair). More commonly, the procedure is performed by injection and entails the application of concentrated platelets to the injured tissue or area, with the intent of initiating and supporting a focal healing response (88). The specific concentration and proportion of blood cells present in PRP,

KEY WORDS:
growth factor; injury; musculoskeletal; regeneration

technique for processing and administration, and pre-peri-post procedural care all serve a role in achieving the desired outcome or response.

Given the propensity of musculoskeletal disorders and the likelihood that sports medicine professionals will encounter individuals who have received or are considering PRP, a baseline understanding of this technology is necessary. Thus, the focus of this article will be to provide an overview of PRP applications for musculoskeletal disorders. Specifically, this article will discuss the bioactive components of PRP, biological mechanisms underpinning use, injection delivery technique, indications and contraindications, as well as the *in vitro* and clinical evidence steering the use of PRP for musculoskeletal disorders. A companion article in this issue will present postprocedural considerations for sports medicine professionals managing individuals following a PRP procedure.

BASIC SCIENCE OF HEALING

A brief, albeit necessary review of the natural healing process (70,97) is first presented to enable an understanding of the biological basis for PRP and to perhaps offer an explanation for the failed healing response seen with chronic conditions and advanced aging. Regarding healing, one must recognize that the musculoskeletal system has different tissue types (e.g., bone, tendon, cartilage, and muscle), each unique with respect to the process of repair or regeneration. Nonetheless, overarching similarities exist and generally involve 3 broad overlapping phases. These phases include inflammation, proliferation, and remodeling or maturation (7). Individuals seeking a more detailed explanation of the healing cascade are encouraged to review previously published resources (7,84).

The inflammatory phase occurs immediately after injury and is associated with hemostasis and focal inflammation (7,84). The coagulation cascade is initiated through thrombocyte (platelet) activation. This, in turn, leads to platelet aggregation, clot formation, and development of a provisional matrix construct, which serves as a scaffold for arriving cells. This step is critical because platelets are activated once they contact the exposed collagen or injured tissue. Activation triggers the release of bioactive factors from the platelet granules (degranulation). Specifically, platelets have 3 types of granules (alpha [α], dense, and lysosomal), each serving different roles. The α granules, when activated, release bioactive substances such as growth factors (GFs) (Table 1). These GFs bind to cell surfaces to promote signaling that initiates cellular upregulation and expression, which is responsible for proliferation and differentiation of cells. In addition, the α granules contain cytokines, which are signaling molecules that serve multiple functions including the regulation of inflammation and chemokines (directional cytokines that attract cells). At this stage, proinflammatory mediators (e.g., prostaglandins) are secreted, which attract neutrophils within a few hours.

Neutrophils, which arrive through chemotactic factors (proinflammatory mediators and cytokines), have a phagocytic effect on the injured

Table 1
Growth factors found in platelet alpha granules and their function

Growth factors in platelet alpha granules (5,77,83,88,103,109)	
Growth factor (GF)	**Function**
Insulin-like GF-1 (IGF-1)	Cell growth, proliferation, and differentiation. Stimulates collagen synthesis. Proliferation and differentiation of mesenchymal cells (connective tissue [e.g., muscle, cartilage, and bone] and blood vessels)
Platelet-derived GF (PDGF)	Enhances collagen synthesis, macrophage activation, proliferation of bone cells, fibroblast chemotaxis, and mitosis. Stimulates angiogenesis and vasculogenesis.
Vascular endothelial GF (VEGF)	Stimulates angiogenesis and vasculogenesis, migration and proliferation of endothelial cells, and stimulates chemotaxis of macrophages and neutrophils
Epidermal GF (EGF)	Accelerates reepithelialization and influences cell proliferation
Transforming GF-β (TGF-β)	Proliferation and differentiation of mesenchymal cells. Stimulates synthesis of collagen, angiogenesis, reepithelialization, and synthesis of protease inhibitors (prevent collagen breakdown). Inhibits osteoclast formation and bone resorption. Key regulator in balance between muscle fibrosis and myocyte regeneration. Some concern exists over profibrotic effects in muscle.
Fibroblastic GF (FGF) numerous subtypes exist	Proliferation of mesenchymal stem cells, chondrocytes, and osteoblasts. Growth and differentiation of chondrocytes, fibroblasts, and osteoblasts. Inhibits osteoclastic actions.
Hepatocyte GF	Angiogenesis, mitogen for endothelial cells, and antifibrotic. Extracellular matrix synthesis. Anti-inflammatory effects.

tissue, promote inflammation through inflammatory cytokines (e.g., interleukin-1β [IL-1β]), and unleash antimicrobial peptides (7,52). The phagocytic neutrophil response is specific to injured tissue, whereas uninjured tissue is protected through protease inhibitors (84). Neutrophils are short-lived (few hours) and undergo apoptosis in the early inflammatory phase. After a few days, IL-1β and GFs (e.g., transforming GF β [TGF-β] and platelet-derived GF [PDGF]) attract monocytes to the area. Monocytes mature to form macrophages, which have a role in debridement, generation of nitric oxide, regulation of inflammation, as well as fibroblast recruitment. Fibroblasts are activated connective tissue cells that produce collagen and other connective tissue components. Thus, they are not specialized and can differentiate into many cell types (e.g., tenocyte and chondrocyte). When activated, macrophages express different functional states (polarization) classified as either M-1 or M-2 based on their microenvironment. M-1 is generally proinflammatory and possesses antimicrobial properties, whereas M-2 is immunomodulatory because it releases the anti-inflammatory cytokine IL-10 (IL-10) and other factors (TGF-β), which promote tissue repair and resolve inflammation. Moreover, in response to the proinflammatory arachidonic acid mediators stimulated immediately after injury, specialized proresolving mediators such as lipoxins form (from platelets and leukocytes) to mitigate inflammation (78).

The proliferative phase occurs within a few days of injury and is responsible for cellular proliferation and differentiation. A concerted effort by the macrophages and GFs occurs to drive angiogenesis (forming or sprouting from existing vessels), vasculogenesis (formation of new vessels), granulation tissue formation, and collagen deposition (through fibroblasts) (66). Vascular endothelial GF (VEGF) and PDGF are responsible for angiogenesis and vasculogenesis, whereas insulin-like GF (IGF) and TGF-β are responsible for the production of collagen, proteoglycans, and other components of the extracellular matrix. In addition, VEGF attracts endothelial cells, which produce nitric oxide and increase blood flow to the site of injury. In addition, fibroblasts focus on synthesizing collagen and a provisional matrix composed of type 3 collagen, fibrin, fibronectin, proteoglycans, and glycosaminoglycans. GFs at this stage prevent degradation and promote further production of collagen through cellular upregulation. Essentially, cells and GFs drive the proliferative phase of tissue repair and may begin to differentiate into the predominant tissue-specific cell type within the first week. In most environments, stem cells and the more differentiated progenitor (e.g., satellite or tendon progenitor) or committed cells (e.g., tenocyte) function to replace cells lost through normal attrition or turnover. In the case of injury, these cells are activated as a means of facilitating repair and regeneration. Assuming that these cells have not become senescent and the microenvironment is appropriate, they will serve their intended purpose.

Toward the latter stages of the proliferative phase, GFs further stimulate fibroblast proliferation, migration, and synthesis of the components of the extracellular matrix. Collagen accumulation reaches a maximum at 2–3 weeks, and a transition to the remodeling phase begins. Degradation and synthesis are balanced, as type 1 collagen begins to replace type 3 collagen, leading to increased strength of the injured tissue. The preliminary extracellular matrix is replaced by an organized matrix of stronger collagen fibrils. This phase is believed to take up to a year for completion. Despite an optimal healing environment, repaired tissue is generally less organized and weaker than uninjured tissue. Thus, the importance of recognizing a contrast between repair and regeneration is of significance, as the latter would be more desirable, albeit not achieved with most normal healing processes.

The natural healing phases are capable of repairing nearly every tissue in the body under the appropriate macroenvironment and microenvironment. Even in the cases of surgical repair, the natural healing cascade is activated. In cases of acute injury, local regulatory mechanisms adjust the magnitude of the inflammatory response so that the amount and duration are adequate for the level of injury. Deviations in the healing process (e.g., aberrant differentiation of fibroblasts) contribute to various pathological conditions such as tendinopathy and OA (7). An important point to note is that the synthesis of GFs and cytokines in one phase acts as a stimulus for progression into the next phase. Persistence of the inflammatory phase, because of elevated proinflammatory cytokines (e.g., tumor necrosis factor alpha [TNF-α] and IL-1β) and accumulation of macrophages may lead to impaired healing and a failed healing response (7).

In addition, obstacles may exist in the healing cascade, which interfere with remodeling (and in some cases, proliferation). These obstacles include, but are not limited to, aged-related changes such as cellular senescence and exhaustion of active stem-cell pools; as well as tissue ischemia and GF declines (e.g., IGF and PDGF) (10,15,34,41,57,61,72,73,108). The obstacles to healing are key examples as to why PRP, which is rich in GFs and cytokines, may be more appropriate than other treatments such as corticosteroids, which are cytotoxic and only serve to reduce inflammation (1,2,6,7). Finally, physical activity may help or hinder the healing cascade. Overzealous attempts at loading tissue too early in the healing phase or insufficient activity in the later stages may negatively influence outcomes. It is in these cases that we may see a propensity toward chronicity and a benefit from biological interventions such as PRP.

WHAT DOES A PLATELET-RICH PLASMA INJECTION ENTAIL?

PRP is an autologous blood product (patient's own blood), processed to

concentrate cells, which are injected back into the patient at the site of injury or pathology. The procedure for a PRP injection will vary by facility, as numerous preparation techniques and commercial available kits can be used. To date, there is no consensus on the best method to prepare a PRP. Interpractitioner idiosyncrasies in the volume of blood procured, platelet concentration, presence of leukocytes and erythrocytes, use of preparation kit versus manual handling, centrifugation steps, activation methods, number and timing of injections, and both periprocedural and postprocedural care lend to large variations in formulations and outcomes. These variations, coupled with the heterogeneity of musculoskeletal presentations, challenge the ability to draw definitive conclusions from the available research. These variations have prompted the development of classification schemas such as MARSPILL. The MARSPILL classification system enhances the ability to standardize procedural terminology and composition of PRP, and the letters in the name designate reference to preparation procedures (e.g., M = manual or hand processed). Table 2 presents an overview of the MARSPILL classification system and is included as a means of enabling the reader to recognize the potential variance in PRP preparation and procedures. The procedure described in this article will be manual (handmade method), without activation components, no kits to remove red or white blood cells, 2 spins on centrifuge, and photoactivation using LED lights. This specific procedure provides the opportunity to present details of the steps and lends to a greater understanding of the process and components of PRP. Moreover, this is the method most familiar to the authors. It is important to recognize that some physicians may use different preparation protocols (30,38,89) (e.g., use of kit to remove leukocytes) based on personal preference, optimization of cell concentrations (e.g., platelets), or what may be best for a specific patient or client.

Table 2
MARSPILL classification system used for platelet-rich plasma injections

MARSPILL classification (64)		
Letter	**Attribute**	**Type**
M	Method	Handmade or machine
A	Activation	Activated
		Not activated
R	Red blood cells (erythrocytes)	Rich
		Poor
S	Number of spin steps on centrifuge	One
		Two
P	Platelet #	2–3, 4–6,6–8, and 8–10x above baseline
I	Image guided	Guided
		Not guided
		Ultrasound or fluoroscopy
L	Leukocyte concentration	Rich
		Poor
L	Light activation	Activated
		Not activated

Before any procedure, the patient is screened for contraindications to PRP (50). Specific contraindications include local or systemic infection, local or metastatic cancer, hemodynamic instability, and platelet disorders such as critical thrombocytopenia and thrombocytosis. Relative contraindications include individuals who are on anticoagulant therapy, have anemia (hemoglobin < 10 g/dL), or those with liver disease that may affect platelet counts (50,95). Regarding sports medicine, the presence of anemia among athletes (21) should be considered when evaluating appropriateness of PRP as a treatment option.

The procedure itself takes approximately 1 hour. Patients first undergo a venipuncture blood draw (usually antecubital [front of the elbow]) to obtain approximately 40 cc of whole blood per treated region. This amount may vary based on practitioner preference or other factors. The blood is obtained using a 21-gauge butterfly needle, as smaller bore needles may lyse (damage) or prematurely activate the platelets (50). The blood is drawn into tubes containing an anticoagulant such as sodium citrate (1cc per 10cc of whole blood) to prevent clotting. This is key because clotting may activate the platelets, which is not desirable at this stage. The procured blood is processed under a laminar flow biological safety cabinet (bio-hood), which uses filtered air and prevents inflow of air to maintain an aseptic environment. The tubes are placed into a centrifuge for 10 minutes of slow spinning at a rate of 1,600 spins per minute, which converts to a relative

centrifugal force of 200*g*. The first spin separates plasma from the red blood cells (which are now located at the bottom of tube). The tube is removed from the centrifuge once spinning is complete, and the product is processed. At this stage, 2 layers are generally visible (Figure 1). The top layer is plasma (clear yellow) and bottom layer is erythrocytes (red). There may be a small, albeit indistinguishable, zone in the middle referred to as the buffy coat, which contains GFs and leukocytes. At this point, the plasma is drawn from the tube, which may contain a very small amount of erythrocytes as well. The retained plasma is then placed into another tube for the second centrifugation at 3,800 RPM (2,500*g*) for 10 minutes. After the second centrifugation step, 2 layers are present with a middle buffy coat (Figure 2). The top layer is platelet-poor plasma, which is generally discarded. Some of the platelet-poor plasma, the remaining middle buffy coat, and some of the bottom layer, which are erythrocytes and platelets, are then resuspended (mixed) to ensure that the buffy coat is not adhered to the wall of the blood tube. Before injection, the tube is placed into an LED light device for photoactivation (Figure 3), which stimulates the anti-inflammatory IL1 receptor antagonist (IL-1RA) and IL-10 cytokines as well as a reduction in inflammatory cytokines (e.g., IL-2 and IL-6) (82,110). It should be noted that the evidence for photoactivation is limited, and 2-arm clinical trials that compare final cytokine concentrations are necessary to conclude a definitive benefit. At this stage, a platelet activator may be added (e.g., thrombin); however, collagen is a natural activator of PRP (30). Thus, when PRP is used for soft-tissue injuries, an activator is not needed (30). The final PRP product will usually contain approximately 5–6cc of concentrated cells (Figure 4). The site of pathology may be injected with a local anesthetic solution before administering the PRP. The anesthetic component of the procedure may also be used to road test the patient by confirming that the site of injection is specific to pain, through testing before and after injection. Resolution of pain after injection confirms proposed pathology and guides the physician to an appropriate injection site. A body of *in vitro* evidence has shown chondrocyte, fibroblast, and tenocyte toxicity to anesthetics such as bupivacaine (Marcaine) or lidocaine (xylocaine) prompting some physicians to avoid use; however, this may be at the expense of a painful experience for the patient (53,106). Greater concentrations (e.g., 2 versus 1% lidocaine) and use of bupivacaine have a more pronounced effect on cellular toxicity (48,106); thus, physicians may elect to use 1% lidocaine as a means of reducing (although not eliminating) risk of cellular toxicity and improving patient comfort. Depending on the site of injection, imaging guidance (fluoroscopy and ultrasound) may be used. In cases of joint pathology such as OA, the injection would be into the joint, whereas tendinopathy generally requires an injection into the tendon sheath in a peppering manner.

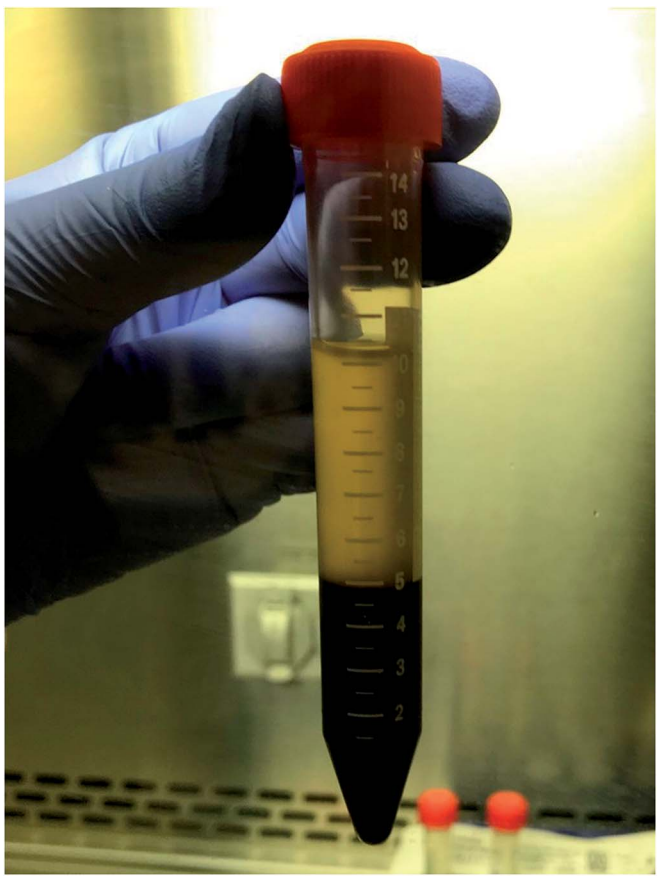

Figure 1. Tube containing blood product after first-slow spin in centrifuge. Clear yellow top layer of plasma and bottom red layer containing erythrocytes.

After the injection, the puncture site is covered with a bandage and ice is applied. The patient is educated on the expectation of an inflammatory response that may last from a few days to a week. Also, the patient is informed about a potential for erythema (redness) and pyrexia (heat) at the puncture site, as well as the importance of pain-free movement and avoidance of complete rest (inactivity) (5,50). Post-procedure analgesic prescriptions are dispensed and patients generally return in 2–6 weeks for a reassessment (50). Given that there are no specific guidelines steering additional injections, the decision is individualized to the patient's specific situation (specific

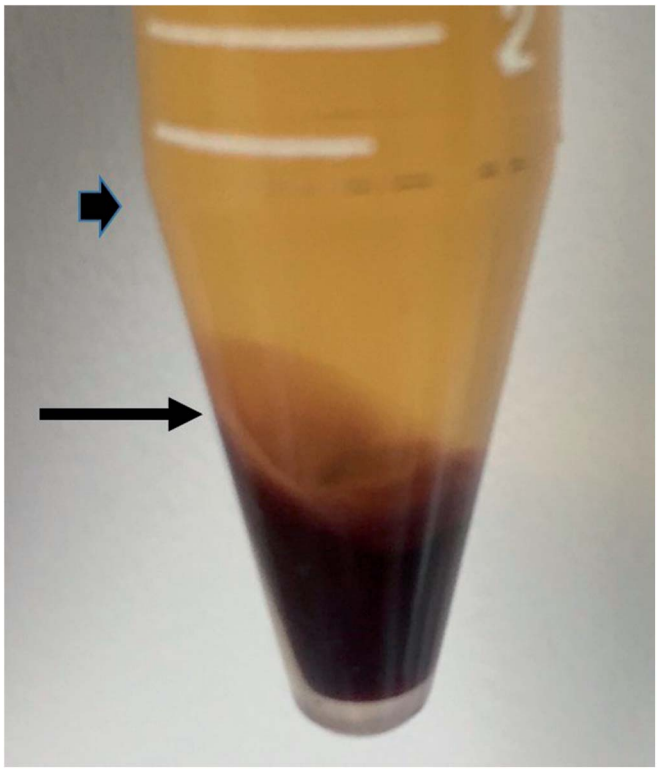

Figure 2. Tube containing blood product after second-fast spin in centrifuge. Clear yellow top layer of platelet-poor plasma (block arrow), as this spin concentrates platelets rich in growth factors at the middle buffy coat (arrow), which also contains leukocytes. Bottom layer contains remaining erythrocytes and platelets.

pathology and level of improvement) (50). Individuals with considerable improvement may not require an additional injection, whereas those with limited improvement may receive additional 1–2 injections. Additional considerations for the management of individuals after a PRP injection are presented in a companion article published in this issue.

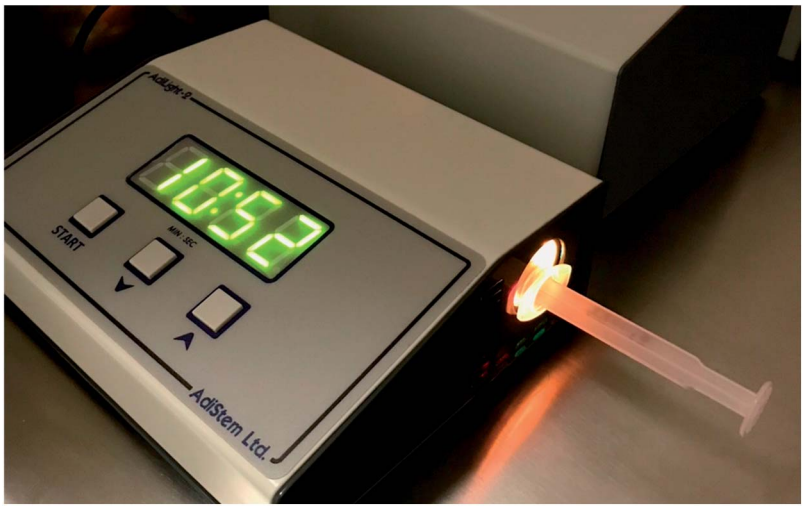

Figure 3. Photoactivation of tube containing final PRP product. PRP = platelet-rich plasma.

PLATELET-RICH PLASMA COMPONENTS

PRP is an autologous blood product derived from processing whole blood in a manner that produces supraphysiological concentrations of cells, namely platelets. Platelets contain a reservoir of GFs (Table 1) including but not limited to PDGF, epidermal GF (EGF), TGF-β, VEGF, fibroblast GF, hepatocyte GF, and IGF. These GFs are released from the α granules in platelets through a process called degranulation. Degranulation occurs when the platelets are activated, which may occur on contact with collagen (e.g., from injured tissue) or through activation agents (e.g., thrombin). Using an activator may lead to a more controlled release of cytokines and GFs (51). The goal of increasing platelet concentrations resides in exponentially increasing GF concentrations, which in the context of injury, should enhance the healing and regenerative process. In a healthy person, baseline platelet counts may range from 150,000 to 350,000 cells per microliter (μL) (83). Standard PRP contains a concentration of platelets that is approximately 3–9 times the baseline values (9,35,40,50,66). It would seem that higher concentrations would be of greater benefit; however, a body of evidence suggests that platelet concentrations may have an inhibitory effect on cell proliferation when they are too high (47,101). In addition to GFs, the α granules contain cytokines and chemokines. These cytokines function in both a proinflammatory and anti-inflammatory manner (Table 3). Fortunately, the anti-inflammatory cytokine IL-1RA is present in greater concentrations than the proinflammatory IL-1β (75).

Erythrocytes and leukocytes are present in varying concentrations dependent on processing procedures. These cells contain cytokines and chemokines that have a role in PRP

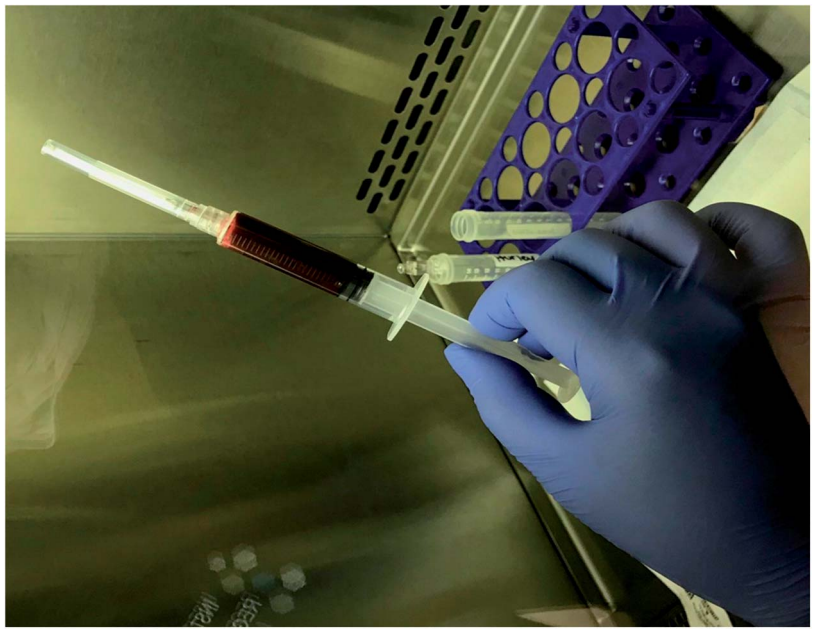

Figure 4. Tube containing final PRP for injection. The red color is due to the inclusion of small amounts of red blood cells. PRP = platelet-rich plasma.

Table 3
Proinflammatory and anti-inflammatory cytokines present in PRP preparations: IL, interleukin; TNF, tumor necrosis factor; RA, receptor antagonist

Cytokines in platelet-rich plasma (6,64,75)	
Proinflammatory cytokines	**Anti-inflammatory cytokines**
IL-1β	IL-1RA
IL-2	IL-4
IL-6	IL-5
IL-8	IL-10
IL-17	IL-13
TNF-α	

Cytokines are a broad category of signaling proteins, and there is some terminology overlap with growth factors and hormones.

PRP = platelet-rich plasma.

outcomes. Some researchers and physicians have advocated a product that is void of leukocytes, based on the contention that these cells evoke inflammation, lend to increased pain and impaired outcomes (23,93,96). Unfortunately, there is uncertainty as to the definitive nature of this contention, particularly as leukocytes serve a key role in the healing cascade (68,78,79,86). Moreover, evidence suggests that GF concentrations are generally higher in leukocyte-rich PRP and that the safety profile is comparable with leukocyte-poor PRP (79,86).

The activation of the inflammatory cascade differs with respect to primed and activated neutrophils (most abundant type of leukocyte) (78). Neutrophils are present in a resting state, and 2 different signals are required to launch an inflammatory reaction (78). The first is a priming signal, which wakes up the neutrophils and usually occurs from chemokines or an inflammatory cytokine. In the case of PRP, the neutrophils may be primed through activated platelets. The priming allows the neutrophils to release an array of substances such as cytokines and to some degree GFs. The second signal, which activates the inflammatory response, is limited without the presence of either an acute injury, infection, or foreign body. Thus, in the context of PRP, activation of neutrophils and the pathway into an excessive inflammatory phase is quite limited (78,79). Moreover, primed neutrophils retain the benefits of having enhanced phagocytic activity and the ability to generate anti-inflammatory cytokines and work in cooperation with activated platelets to form the anti-inflammatory pro-resolving molecule lipoxin (19,78,79).

Although erythrocytes are generally discarded and the small amounts retained are used in part for resuspension, some benefits may exist. For example, erythrocytes serve a valuable role in platelet function and in the production of regulatory molecules such as nitric oxide (22). Nitric oxide promotes vasodilatation and may assist GFs such as IGF in exerting its anabolic effects (14). Erythrocytes have other functions such as helping to generate thrombin, which is a potent stimulator of platelet activation and degranulation (79). Finally, erythrocytes contain glutathione, an antioxidant that has the ability to disable some of the free radicals at the site of injury (44).

Regarding bioactive concentrations, PRP preparations will contain varying concentrations dependent on processing procedures. PRP contains blood cells (platelets, leukocytes, and erythrocytes), GFs, proinflammatory and anti-inflammatory cytokines (Table 3), chemokines, and various

other substances such as adhesion factors, fibroblasts, and $CD34^+$ stem cells (5,75). Chemokine examples include the stem cell navigating or homing agents referred to as stromal-derived factor-1 (SDF-1) alpha and stem-cell factor. These chemokines attract stem cells to the area to assist with regeneration (64). $CD34^+$ stem cells are multipotent hematopoietic stem cells recruited by macrophages and specific chemokines such as SDF-1 and can differentiate into osteogenic or endothelial lineages (5,87).

MECHANISM OF ACTION

The biological basis underpinning the use of PRP for musculoskeletal injuries primarily stems from the ability of activated platelets to release bioactive components (GFs and cytokines) from the alpha granules in concentrations higher than baseline or whole blood. Degranulation, as stated, exposes the GFs and cytokines to the cells at and near the region of injection. These activated bioactive components bind to cell membranes triggering signaling pathways. Signaling from the bound receptors on the cell membrane activates the cell and through secondary messengers upregulate gene expression specific to the cell and GFs. The ultimate benefit from a PRP injection resides in obtaining higher concentrations of GFs and anti-inflammatory cytokines than what is produced as part of the normal healing process. Furthermore, PRP has chemotactic agents that attract circulating cells, which participate in the regenerative process.

Numerous types and levels of cells are involved in the healing process and include stem cells, which have the ability to differentiate into a more specialized cell (e.g., myocyte, chondrocyte, or tenocyte). Differentiation of stem cells into a more specialized cell requires several stages, controlled by messages sent to the cell's DNA, the physical environment or niche, and signals from neighboring cells through bioactive factors or physical contact. Typically, adult stem cells will differentiate into the cell types of the tissue in which they reside (e.g., stem cell from the bone marrow, i.e., hematopoietic (blood forming) will differentiate into a blood cell). Region-specific progenitor cells are also involved, which are more specialized than stem cells and generally differentiate into a specialized (target) cell in the local environment (e.g., satellite progenitor cell differentiates into a specialized myoblast or a tendon progenitor cell differentiates into a mature tenocyte). A difference between stem cells and progenitor cells is the stem cells' ability to self-renew. A key point here is that these cells generally are dormant and activated on injury or stimulus by both mechanical (injury or mechanotransduction) and chemical factors (e.g., GFs or hormones). For example, satellite cells are signaled with exercise that involves overload, as well as through GFs and cytokines. In addition to the stem and more specialized progenitor cells, region-specific cells are upregulated as well, which include tenocytes, osteoblasts, chondrocytes, and fibroblasts.

A point to consider in many chronic conditions such as tendinopathy is that there is a failed healing process. Tendon progenitor cells may differentiate into chondrocytes or adipocytes as opposed to tenocytes in cases of chronic tendinopathy. This failed healing process may be augmented by exposure to GFs and cytokines found in PRP preparations. For example, GFs from PRP will bind to the cellular membrane of the tendon progenitor cells. Once binding occurs, signaling lends to gene expression for collagen synthesis through the activation and proliferation of tenocytes. Furthermore, GFs lend to gene upregulation that will mediate angiogenesis and vasculogenesis, further contributing to the regenerative process. In cases of inflammatory conditions or chronicity, the hope is that a more balanced presence of cytokines (e.g., increased anti-inflammatory cytokines) from the PRP preparation will modulate the inflammatory process and regulate the healing environment. Table 4 presents an overview of PRP components and effects.

EVIDENCE SURROUNDING PLATELET-RICH PLASMA USE

In the past decade, a surge of research has attempted to unravel the effects and benefits of PRP. Research in the form of *in vitro* laboratory studies on human and animal tissue, in vivo animal studies, and clinical evidence exists. The intent of this section is to provide a narrative overview of the available evidence; however, the section is not meant to be an exhaustive review, as key systematic reviews with meta-analyses are referenced to provide the interested reader greater detail.

In vitro evidence is presented primarily to coincide with the proposed mechanism of action for PRP with respect to cellular changes and immunomodulatory effects. The clinical evidence is based on the more common musculoskeletal conditions, which were selected in the form of comparative systematic reviews with meta-analysis as well as randomized controlled trials (RCTs) and case series. Independent RCTs are presented in cases where adequate systematic reviews were not available or in cases where systematic reviews were limited in scope. Case series are presented to highlight situations where follow-up imaging has shown anatomical changes.

IN VITRO EVIDENCE

In vitro studies of human tissues have evaluated the effects of PRP on osteoarthritic chondrocytes, subchondral progenitor cells, mesenchymal stem cells, tenocytes from degenerative rotator cuff tears and various body regions, as well as ligaments. Despite variations in procedure, concentrations, and exposure time, results are consistent with respect to favorable effects.

Regarding OA, evidence suggests that exposure to PRP *in vitro* leads to regenerative cellular changes and a reduction in catabolic activity (e.g., matrix metalloproteinase-1) (96). Specifically, osteoarthritic chondrocytes exposed to PRP (from healthy donors and autologous preparations) had reduced inflammatory markers (e.g., IL-1β and TNF-α), increased GFs and chondrocyte

Table 4
Summary effects of platelet-rich plasma

Platelet-rich plasma and summary effects (5,40,64,78,79)	
PRP components	**Summary effects**
Platelets	Degranulation of alpha and dense granules. Alpha granules' primary effect is the release of growth factors, cytokines, and chemokines
	Dense granules, such as serotonin produces vasoconstriction and histamine increases capillary permeability, and attract and activate macrophages
Growth factors	Recruitment, activation, proliferation, and differentiation of cells (stem and progenitor) involved in tissue regeneration
	Establish and support blood supply
Cytokines	Signaling molecules that are proinflammatory and anti-inflammatory
Chemokines	Helps with homing and navigation of stem cells and growth factors
Leukocytes	Inflammation
	Neutrophils (in cooperation with platelets) produce lipoxins (anti-inflammatory)
	Antimicrobial
Erythrocytes	Nitric oxide (vasodilation)
	Produce glutathione (antioxidant)
	Activate platelets
Fibroblasts	Connective tissue cell that synthesizes the extracellular matrix and collagen

PRP = platelet-rich plasma.

proliferation, and reduced apoptosis (74,96,100). Cultured subchondral progenitor cells have a favorable reaction as well when exposed to PRP, with evidence suggesting migration and differentiation of the cultured cells, as well as an increase in type 2 collagen and proteoglycan concentrations (63). Moreover, when human mesenchymal stem cells (multipotent functions [differentiate into numerous tissue types]) are cultured in PRP, there is an increase in cell proliferation and increased expression of chondrogenic markers (71). These findings have implications for OA and the potential inclusion of other RM procedures such as mesenchymal stem cells for the treatment of degenerative conditions.

Tendinopathy (the presence of degeneration, tearing, or inflammation of the tendon) often results in a failed healing response owing to poor blood supply, slow cell turnover, and purported differentiation of tendon progenitor cells into adipocytes or chondrocytes. *In vitro* evidence has indicated that PRP increases tenocyte number and vascularity in culture (8). Although numerous tissue sites have been studied, a considerable body of evidence has investigated the effects of degenerated rotator cuff tendons cultured in PRP with favorable results (23,54,55). For example, cultured tenocytes from degenerated rotator cuff tendons have shown enhanced gene expression, synthesis, and proliferation of the tendon matrix (54,55). Moreover, evidence from moderately degenerated rotator cuff tendons has shown that PRP promotes normal collagen matrix synthesis and decreases cytokines associated with matrix degeneration and inflammation (23). Interestingly, in the aforementioned study, no changes occurred in severely degenerated tendons, and changes seen with moderately degenerated tendons were more pronounced with PRP containing reduced leukocyte concentrations. In contrast to the findings of the previous study, Parrish et al. (79) compared leukocyte-rich and leukocyte-poor PRP on healthy tenocytes and reported leukocyte-poor PRP to be comparable with whole blood, whereas leukocyte-rich PRP stimulated greater tendon cell proliferation than whole blood.

A sufficient body of evidence has shown that cells exposed to corticosteroids experience reduced collagen organization, impaired fibroblast viability, and depletion of cell pools (1). Muto et al. (76) investigated the detrimental effects of a corticosteroid on human rotator cuff cells and sought to determine whether PRP can protect the cells. A comparison of cells exposed to corticosteroids alone was compared with corticosteroids plus PRP and a control without any additive. Results indicated that cells exposed to a corticosteroid and PRP were similar to controls, whereas cells exposed to the corticosteroid alone

had decreased viability and apoptosis. These findings are supported by an additional study (55) that identified a protective effect of PRP on degenerated tenocytes from rotator cuff tendons. In this study, PRP did not interfere with the anti-inflammatory effects of the corticosteroid and reduced the deleterious effects of the corticosteroid on cell viability (55).

Regarding ligaments, few *in vitro* investigations exist. In terms of ligament pathology, the degree of involvement ranges from sprains to tears, and failed healing is more likely to present with complete tears and/or insufficiency. Thus, ligament does not follow the same clinical pathway as tendons. One investigation cultured fresh cells from anterior cruciate ligaments harvested during surgery and reported increased cell viability when exposed to autologous blood, suggesting a potential role of PRP in ligament healing (36). *In vitro* studies on muscle cells, however, are more common and indicate that PRP application results in proliferation, satellite cell differentiation, and angiogenic factors (13,69).

CLINICAL EVIDENCE

Although *in vitro* evidence is promising and provides biological evidence supporting the proposed mechanism of action for PRP, extrapolating these findings to a heterogeneous patient population must be done with caution. Fortunately, a body of evidence exists to describe the merit and limitations of PRP in the management of musculoskeletal disorders (Table 5). This section provides an overview of the available evidence for the more common conditions treated with injectable PRP and is not meant to be an all-inclusive discussion. Studies that used bone marrow aspirate or adipose grafts with PRP were not included, as the addition of hematopoietic cells would likely produce better outcomes than PRP alone and confound the interpretation of evidence in favor of PRP. In addition, a discussion of PRP-enriched scaffolds or gels used to augment surgical procedures is beyond the scope of this article and may be found in previously published studies (77,103).

A body of evidence suggests that PRP may have a role in the treatment of OA. A brief summary of the evidence is provided for PRP at the knee, shoulder, and hip. Regarding the knee, evidence from 2 systematic reviews with meta-analysis, suggest that PRP produces superior outcomes when compared with placebo (no intervention), saline, and hyaluronic acid (HA) (17,25). The outcome measures generally used in the available studies consist of pain, stiffness, and function. Of the studies included in the systematic reviews, anywhere from 1 to 4 injections were compared without evidence of a dose-dependent relationship. In one systematic review, adverse events (local reactions of inflammation and hyperthermia) were associated with an increasing number of PRP injections (17); however, a more recent review reported that PRP did not lead to an increased risk of adverse events when compared with saline or HA (25). In both reviews, superior results were identified as early as 2 months and lasted for up to 1 year, which was the terminal follow-up established by the studies. Shen et al. (92) performed a meta-analysis of RCTs comparing PRP with other injections (HA, corticosteroid, and saline) among patients with knee OA and found that PRP produced better results at 3–6 and 12 months. A RCT of patients with knee OA included one group that received 3-weekly injections of PRP and another group that received 3-weekly injections of HA, as well as a third group that received both injections (26).

Additional evidence from RCTs are comparable with the systematic reviews, albeit provide more detail of research procedures (18,81). In one double-blinded RCT, 78 patients with bilateral knee OA were randomized to receive 1 injection of PRP, 2 injections of PRP, or a saline injection (81). Results indicated that within a few weeks, the PRP groups had significantly improved pain, stiffness, and function (based on the Western Ontario and McMaster University Osteoarthritic Index (WOMAC), compared with the control group. Improvements persisted for up to 6 months, which was the final follow-up; however, the authors suggest that the results began to deteriorate at 6 months. No difference in outcomes was found when comparing the number of PRP injections. In another investigation, 4 total injections (once a week) compared PRP with HA (18). In the aforementioned study, both groups improved; however, PRP was superior to HA, based on WOMAC scores up to 24 weeks after the injection (18). In addition, HA was not found to be effective in advanced OA, whereas PRP results did not differ between severities. In another study, acetaminophen (Tylenol) was compared with PRP for a duration of up to 24 weeks (93). A 500-mg dose was taken every 8 hours for 6 weeks in one group, and one PRP injection was administered every 2 weeks for a total of 3 injections over 6 weeks in the second group. Results suggested a superiority of PRP over acetaminophen regarding quality of life, pain, and function. Finally, a comparison of a single PRP procedure with a single corticosteroid injection in an RCT of patients with advanced knee OA reported improvement in both groups (56). Pain, function, quality of life, and health perception were investigated at 1–3, and 6 months. Improvement in both groups was documented; however, the PRP group experienced better outcomes with respect to quality of life and health perception at 3 and 6 months. Although pain and functional differences between groups were not statistically significant, a trend toward superior outcomes was present for the PRP group according to the authors.

A paucity of evidence exists for PRP interventions regarding hip and shoulder OA when compared with the knee. Doria et al. (31) compared 3 PRP injections with 3 HA injections among patients with hip OA and found improvement in both groups at 6 and 12 months. A between-group comparison indicated no superiority of the 2 interventions. Outcome measures included pain rating and the WOMAC. Results indicated that 3-weekly intra-articular PRP injections offer a significant clinical improvement in pain that was superior to the HA

Table 5
Summary of clinical evidence

Injury or disorder	PRP clinical evidence overview
Osteoarthritis: knee-hip-shoulder (17,18,25,26,31,56,60,81,92,93)	PRP offers greater benefit than other injections such as HA, corticosteroid, and saline
Rotator cuff disorders (58,85,90,91)	[a]PRP improved pain and function greater than dry needling and corticosteroid injection. Improved tendon anatomy.
Lateral epicondylalgia (3,12,42,45)	[a]PRP improved pain and function greater than corticosteroid
Ulnar collateral ligament sprain (29)	[b]Improved pain and function with reconstitution of injured ligament
Gluteal tendinopathy (39)	[b]PRP improved pain and function greater than a corticosteroid injection
Patellar tendinopathy (32,33,45,49)	[a]PRP improved pain and function as well as tendon architecture.
Achilles tendinopathy (27,28,62)	[a]PRP improved pain and activity as well as tendon architecture.
Plantar fasciitis (11,94,104)	[a]PRP improved pain and function as well as tissue anatomy
Acute muscle strain (16,46,49,80,88)	PRP leads to earlier return to play, reduction of impairments, and improvement in healing
Discogenic pain (4,67,99)	[b]PRP improved pain, disability, and function

[a]Results not consistently superior to other interventions.

[b]Limited comparative studies exist to determine superiority to other interventions

HA = hyaluronic acid; PRP = platelet-rich plasma.

group and the group that received both injections throughout the follow-up periods of 2, 6, and 12 months. The addition of PRP + HA did not improve outcomes compared with PRP alone. Finally, increased IL-10 (anti-inflammatory cytokine in PRP) was correlated with decreasing levels of pain. Regarding shoulder OA, one study compared PRP with corticosteroid injections or ultrasound in a group of patients randomized to 1 of the 3 groups (60). Results indicated a superiority of a single injection of PRP with respect to range of motion, pain, and function at 6 and 12 weeks.

Regarding soft-tissue injuries, a body of research has investigated tendon disorders (including tendinopathy and tears), fasciopathy, muscle injury, ligament trauma, discogenic pathology, and sacroiliac joint pain. The evidence for PRP in these areas is limited primarily to RCTs and case series, as existing systematic reviews at this time do not yield enough studies to identify a consensus for clinical evidence.

Rotator cuff pathology seems to be of greater interest with respect to published studies. One RCT compared PRP with a corticosteroid injection among individuals with partial rotator cuff tears (91). Results indicated that both groups improved over time. At week 12, PRP was superior for pain and function; however, groups were comparable by 6 months. Rha et al. (85), in an RCT, compared 2 PRP injections with 2 sessions of dry needling among patients with supraspinatus tendinopathy or partial tear. In this study, PRP produced superior results for pain and disability at 6 weeks and 6 months. In another study, PRP was compared with a saline injection among individuals with chronic rotator cuff tendinopathy (58). In this study, both groups had improved function, pain, and quality of life (58). At the 3-week up to 1-year mark, no differences were present between groups. Finally, a case series of 20 patients with symptomatic partial rotator cuff tears received an injection of PRP. At the 8-week follow-up point, diagnostic ultrasound showed healing and statistically significant improvements for pain and function in 17 of 20 patients (90).

The effects of PRP on tendon disorders (grouped together) throughout different areas of the body have been reported in previously published systematic reviews with meta-analysis (20,37). In one meta-analysis, the effect of PRP on pain was evaluated for tendinopathy only (37). In this analysis, the authors reported good evidence for pain reduction from PRP in comparison with control interventions such as corticosteroid injection, saline, anesthetic, and dry needling. The authors also reported a superiority of leukocyte-rich PRP over leukocyte-poor PRP.

A systematic review for lateral epicondylitis identified 9 PRP studies (3). A majority showed improved clinical satisfaction, and of the 9 studies, 3 compared PRP with corticosteroid injection. Of the 3 studies, 2 showed no difference between PRP and corticosteroid injection. A limitation of the 3 studies exists

with respect to limiting the terminal point of assessment to 3 months, as evidence suggests that pain relief will occur earlier in corticosteroids but drops off with time (45). The third study had a longer follow-up of 1–2 years, which showed improved pain and function in the PRP group compared with the corticosteroid group (45). Moreover, the study results indicated that at the 2-year follow-up, a steady decline in improvement for the corticosteroid group had occurred, whereas the PRP group maintained improvements.

Studies performed on Achilles tendinopathy have generally shown mixed results of PRP when compared with placebo; however, a discussion of study specifics offers greater insight (27,28). In the aforementioned studies, the subjects performed eccentric training in both groups with one group assigned to PRP and the other saline. Patients were followed for a year and although improvements in pain and activity were noted, there was no significant difference between groups (28). In the 1-year follow-up, there were improvements in ultrasound tendon structure in both groups but no superiority of PRP (27). The most plausible explanation for the lack of finding here resides in evidence of favorable benefits from eccentric training, suggesting that PRP may not have an additive benefit. Krogh et al. (62) compared PRP with saline for Achilles tendinopathy and found that PRP injection did not result in an improved VISA-A score (self-report Achilles tendon outcome measure tool that assesses pain, mobility, and life participation) over a 3-month period in patients with chronic Achilles tendinopathy when compared with placebo. The only secondary outcome demonstrating a statistically significant difference between the groups was change in tendon thickness; this difference indicates that a PRP injection could increase tendon thickness compared with saline injection. In contrast to the above finding, a 3-group RCT was completed to compare 4 PRP injections with one group that received a high-volume saline injection and another with low-volume saline (12). All 3 groups also performed eccentric training. Results generally indicated that PRP was superior to control and led to reduced thickness and improved activity levels. Finally, in a case series of patients with chronic Achilles tendinopathy, a single PRP injection produced meaningful changes in pain and function as well as improved tendon anatomy (42).

A meta-analysis of RCT studies was performed to compare PRP, dry needling, and extracorporeal shockwave therapy for patients with chronic patellar tendinosis (32). The VISA-P (a patellar tendinopathy outcome measure that assesses pain, mobility, and life participation) was used as the primary outcome measure. Analysis showed no significant difference in mean VISA-P scores between groups at the 3-month follow-ups; however, PRP was significantly better than other groups at the 6-month point. In one case series, the effects of PRP on 36 patients with patellar tendinosis were investigated (45). In this study, evidence suggested that individuals were more likely to respond to PRP in terms of improvement on the VISA-P and pain if they did not have previous treatments such as corticosteroid injection or surgery. In another case series, 6 patients with chronic patellar tendinosis underwent 3 PRP injections and within 2 weeks began to show improved tendon appearance on diagnostic ultrasound (33). Also, immediately as well as the 6-month and 1-year follow-up, all 6 patients reported decreased pain, improved function, and clinically important change based on global rating of change (33,59).

The effects of PRP on plantar fasciitis were reported in 2 separate meta-analyses. (94,104). Yang et al. (104) reported little to no difference for pain and function up to 12 weeks when comparing PRP with a corticosteroid injection. However, at 24 weeks, PRP was superior, indicating a benefit that may gradually occur over time. Singh et al. (94) in a similar meta-analysis compared corticosteroid with PRP injections and found significantly better improvements in pain and function for the PRP group at 3 months; however, earlier and later time points showed no differences.

The effect of a single PRP injection was assessed in a case-series investigation of 9 patients with plantar fasciitis; all 9 patients were recalcitrant to previous treatments including nonsteroidal anti-inflammatory drugs, physical therapy, immobilization, and a corticosteroid injection. Patients were reassessed as early as 1 week and up to 1 year. At the 2-month follow-up, 6 of 9 patients were asymptomatic, and by 1 year, 7 of 9 were pain-free and diagnostic ultrasound indicated structural improvements (reduced thickness of the plantar fascia) (11). One patient in the aforementioned study required a second PRP injection.

Finally, with regard to chronic gluteal tendinopathy, a superiority of PRP has been shown when compared with a corticosteroid injection for reducing pain and improving function (39). Interestingly, no differences were present between the groups at the 2- and 6-week follow-up points. However, at the 12-week terminal point of assessment, considerable differences were present in favor of PRP. In another study, the efficacy of PRP with needle tenotomy for gluteal pathology (tendinopathy or partial tears) was assessed among individuals who were recalcitrant to previous interventions (65). In this study, improvements in function and mobility were noted at a mean follow-up time of 19.7 months. A limitation of the study was the lack of a comparison group; however, all subjects were previously recalcitrant to other treatments.

Regarding muscle injury, natural healing often takes place with fibrosis. Although it is expected that PRP would be of benefit, some concern over TGF-β is noted given the propensity for this GF to facilitate fibrosis in muscle (88). Grassi et al. (46) performed a systematic review and meta-analysis to determine the effects of PRP on acute muscle injuries in athletes. Results indicated that athletes who received PRP returned to play earlier than other interventions; however, limited evidence was present for reinjury

reduction and other outcome measures. Bubnov et al. (16) compared PRP with other conservative treatments and reported a superiority of PRP for pain reduction and physical recovery. In addition, diagnostic ultrasound indicated faster muscle regeneration in the PRP group (16). Regarding conservative interventions, a meta-analysis compared PRP with conservative interventions for acute hamstring injury and found that PRP was inferior to eccentric exercises and not different from control interventions (80). One RCT compared PRP with rehabilitation to rehabilitation alone for acute hamstring injuries and found that a single PRP injection combined with a rehabilitation program was significantly more effective in treating hamstring injuries than a rehabilitation program alone based on return to play and pain severity (49).

Deal et al. (29) investigated the effect of PRP on 25 athletes with grade 2 medial ulnar collateral ligament injuries. The athletes received 2 PRP injections, physical therapy, and a varus loading elbow brace. Follow-up magnetic resonance imaging found reconstitution of the ligament plus reduced pain and improved stability in 23 of the 25 patients.

Finally, the effects of PRP (intradiscal) have been studied on patients with symptomatic disc pathology with promising, albeit premature clinical results (4,67,99). Of the 3 clinical studies, one was an RCT with blinding (99). In this study, a single PRP injection was compared with a control group that received contrast only. Results indicated a superiority of PRP for pain, function, patient satisfaction, and disability beginning at the 8-week follow-up and extending up to 1 year. The patients in this investigation reportedly had chronic pain and were recalcitrant to previous conservative interventions. The remaining 2 studies were case-series investigations, which showed improvements in pain and disability as early as 1 month and extending into the terminal data collection points of 6 months (4,67). Regarding pathology, no indication of change has been reported. Of the 3 studies, only one (6 patients) evaluated structural change based on magnetic resonance imaging and radiograph evaluation, and found no change at the 4-month follow-up (4). No adverse events or progression of disk herniation was reported in any of the studies.

In summary, the goal of PRP is to enhance the recruitment, proliferation, and differentiation of cells involved in tissue regeneration and recovery (Table 4). Armed with concentrated GFs and anti-inflammatory cytokines, PRP exposes areas of injury or degeneration to a biologically enhanced healing environment. The degree to which these changes are experienced is highly variable, and much of the evidence pertaining to cellular proliferation is based on *in vitro* studies, which are limited in their translation to the in vivo clinical environment. Nevertheless, clinical evidence exists in favor of PRP as a treatment option for tendinopathy, ligament injury, OA, rotator cuff tears, plantar fasciitis, and discogenic pain. See Table 5 for an overview of clinical evidence for the use of PRP on musculoskeletal conditions.

In general, many of the investigations compared PRP with corticosteroids or HA and found a superiority of PRP. With respect to OA, the benefits seem compelling at the hip, knee, and shoulder, particularly in light of side effects of alternative interventions such as corticosteroid injections. Contrasting results in the 2-arm studies seem to be present at the rotator cuff, patellar and Achilles tendons, and plantar fascia, which may be due to the heterogeneity of the pathology and PRP procedure, further highlighting the need for a more standardized classification system. As expected, case-series investigations for plantar fasciitis, Achilles and patellar tendinopathy, rotator cuff, and ulnar collateral ligament of the elbow were favorable for PRP given the retrospective nature of these studies. Of particular interest are the imaging-based finding of anatomical improvements in soft-tissue structure; however, many of these reports are case-series investigations limiting causal assumptions. From the perspective of time, it does seem that PRP offers more stable long-term benefits; however, the early or immediate benefits may not be substantial in comparison with other interventions.

It is important to evaluate evidence with an understanding that a lack of superiority coupled with significant improvement is a positive finding. Improvement is ultimately the goal and when choosing between comparable interventions, one must evaluate other variables such as safety profile and cost. For example, a clinical decision comparing corticosteroids with tendinopathy should take into account the fact that corticosteroids may decrease tendon cell viability; reduce type 1 collagen expression and upregulate nontenocyte genes (107). PRP, on the other hand, is not associated with these side effects, and evidence suggests that the addition of PRP to a corticosteroid injection may reduce the negative effects on tendons (105). From a safety perspective alone, PRP is a better option, and those who choose a corticosteroid injection should consider the potential negative effects. Weighing the cost of a PRP injection over the benefit is an individual choice. As an intervention, PRP is not a covered service by most insurance plans, and the average per patient cost (total costs PRP/# patients receiving PRP) has been estimated at $1,755 (109); however, this cost takes into account the possibility of multiple injections. A single PRP injection in an outpatient office is considerably less expensive. Nevertheless, insurance-covered services are rarely without costs, particularly in conditions that are refractory.

CONCLUSION

The enthusiasm for an intervention that harnesses the body's self-healing capacity is supported by a growing body of literature with promising clinical results. A challenge in interpreting contemporary evidence for PRP is the heterogeneity of pathologies and procedures, which is likely to improve with classification systems in place and standardization of techniques. Although biological plausibility inarguably exists in support of PRP preparations, there is still much to

learn with respect to those who are more likely to benefit from these interventions. Thus, clinical decision-making rules should be derived and validated. In the absence of a clear contraindication, there seems to be little downside to the use of PRP with the exception of a transient inflammatory response and economic concerns. PRP is rarely covered by insurance, so the risk of a failed or ineffective injection resides in cost (77). On a more promising note, PRP has an excellent safety profile and is void of the risks attributed to other interventions such as corticosteroids and opioids. Moreover, PRP requires little to no downtime and may be concurrently administered with physical activity interventions. With further research and understanding, PRP may bridge the "mainstream" gap between conservative and more aggressive surgical interventions and enter the health care reimbursement realm. For those individuals with musculoskeletal injuries that have been recalcitrant to conservative care and have a desire to remain active with exercise or sports, PRP may be a viable option.

KEY POINTS

- PRP is an autologous blood product that is processed and injected into the site of injury or pathology.
- PRP contains GFs, fibroblasts, cytokines, and chemokines in supraphysiological concentrations that harness the body's natural healing process.
- PRP promotes neovascularization and increases blood supply necessary for the proliferation and differentiation of cells that promote tissue regeneration.
- Clinical evidence identifies PRP as a potentially beneficial intervention for tendinopathy, OA, discogenic pain, and acute muscle injuries.
- A paucity of evidence exists to determine clinical criteria predictive of improvement from PRP.
- PRP has an excellent safety profile and requires little to no downtime from activity.
- PRP is typically not a service covered by insurance.

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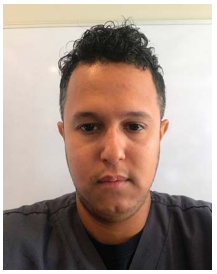

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