Musculoskeletal Medicine

Applications of Platelet-Rich Plasma in Musculoskeletal and Sports Medicine: An Evidence-Based Approach

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This article aims to provide a comprehensive review of the current literature that pertains to the therapeutic use of autologous platelet-rich plasma (PRP). The basic science literature regarding the role of growth factors in mediating the healing process and the laboratory data from in vitro and in vivo studies that evaluated PRP are reviewed. Subsequently, the current evidence regarding PRP efficacy from animal models, human surgical studies, and human clinical studies is presented. A critical analysis of the literature follows, and the article concludes with the authors' perspectives on the state of PRP as a potentially efficacious bioregenerative treatment option for musculoskeletal and sports medicine applications. The relevant articles in this review were obtained via PubMed literature searches for PRP publications that pertain to musculoskeletal and sports medicine conditions. This article is not intended to be a formal meta-analysis.

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INTRODUCTION

Regenerative biomedicine is progressively emerging at the forefront of medicine. This innovative field includes interventions such as the use of platelet-rich plasma (PRP), mesenchymal stem cells, extracorporeal shock wave treatment, sclerosing agents, nitric oxide, and matrix metalloproteinase.

Advancements in the study of these novel bioactive therapies have occurred during the past 2 decades. Recently, the body of literature has grown at a rapid pace, and we are learning a great deal about the potential for these regenerative therapies. Several medical disciplines, including plastic surgery, dentistry, otolaryngology, and spine surgery, have been using these concepts to deliver growth factors to optimize healing. Applications in physiatry, orthopedics, and sports medicine are currently being developed, and regenerative biomedicine is rapidly becoming an exciting and promising treatment option in musculoskeletal medicine. However, much remains to be learned in this emerging field.

In this article we will focus on PRP, a bioactive regenerative therapy that has garnered significant attention in recent years. Results of animal studies have demonstrated the efficacy of PRP in accelerating the healing process after muscle [1], ligament [2], joint [3], and tendon [4,5] injuries. Human clinical trials are emerging alongside numerous anecdotal cases that demonstrate the promise of this innovative therapy, which likely will play a major role in shaping the landscape of sports medicine.

NORMAL BIOLOGIC HEALING RESPONSE

Wound healing cascade involves 3 phases: (1) the inflammatory phase, (2) the proliferative phase, and (3) the maturation and/or remodeling phase. The initial phase, the inflammatory phase, occurs in the first week after injury and involves hemostasis and recruitment of inflammatory mediators. Tissue injury activates cyclooxygenase-2 and leads to vasodilation. Growth factors (discussed later in this article) attract macrophages and fibroblasts. The proliferative and repair phases follow in the next days to 2 weeks, with formation of extracellular matrix with granulation, contraction, and epithelialization. The remodeling phase follows up until about 1

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year after injury, when collagen and scar tissue production takes place. Type I collagen replaces proteoglycan and fibronectin to form a more robust matrix with increased tensile strength [6-8].

Soft-tissue or tendon healing generally involves angiogenesis, cell proliferation, deposition of extracellular matrix, remodeling, and maturation. Various growth factors are stimulated in the process of repair and remain active during the healing stages and will be discussed later in this article. They have important roles in cell regulation, differentiation, proliferation, chemotaxis, and matrix synthesis [6,9,10]. For example, Gulotta and Rodeo [6] describe the stages of rotator cuff healing, during which growth factors are expressed 5-14 days after injury in the repair phase. During this time, the growth factors serve to promote cell proliferation and matrix production.

ROLE OF BIOLOGIC GROWTH FACTORS

After injury, platelets are on the front line and have a critical role in mediating healing by releasing growth factors from their α granules. The growth factors are small peptides that bind to membrane receptors and promote downstream biologic pathways. These growth factors include insulin-like growth factor (IGF-1), transforming growth factor (TGF-β), platelet-derived growth factor (PDGF), vascular endothelial growth factor, and basic fibroblast growth factor (b-FGF). Hepatocyte growth factor, epidermal growth factor, cytokines, chemokines, and metabolites also appear to be involved [11,12] (Table 1). The dense granules of platelets also have a role in tissue regeneration and can release serotonin, adenosine, dopamine, calcium, histamine, adenosine diphosphate, adenosine triphosphate, and catecholamines [12,13].

Together, the growth factors influence chemotaxis and cell migration via chemical mediators. These growth factors also can induce mitosis, extracellular matrix production, and angiogenesis. Moreover, they signal cells to proliferate and they influence maturation, differentiation, and ultimately tissue repair [1,14-16].

Menetrey et al [17] found that b-FGF and IGF-1 played a role in myogenesis and muscle regeneration in vivo in a mouse model. Therefore b-FGF and IGF-1 may have implications in recovery from muscle strains. The growth factors appeared to influence myoblast proliferation and differentiation. At 1 month, improved healing and increased fast-twitch strength were demonstrated in injured mice gastrocnemius muscles that were lacerated, repaired, and then serially injected with b-FGF and IGF-1 at days 1, 3, and 5 after injury. The contralateral leg was similarly injured and injected with the same volume of a physiological solution. Contractile measurements and histologic features were among the variables assessed. Histologic changes were attributed to the serial injections compared with the control group. All mice had the same time interval of serial injections, and comparisons were not made to single injections [17,18].

With regard to cartilage regeneration, growth factors appear to have chondroinductive effects. TGF-β contributes to chondrocyte phenotype expression and mesenchymal stem cell chondrogenic differentiation. IGF also has anabolic properties in cartilage regeneration. In addition, PDGF influences chondrocyte proliferation and proteoglycan synthesis [14].

Table 1. *Growth factors involved in the healing process**

Growth Factor	Function
IGF-1	Early inflammatory phase
	Anabolic effects
	Protein synthesis, proliferation of myoblasts and fibroblasts
	Enhances collagen and matrix synthesis
	May modulate swelling
TGF-β	Proinflammatory
	Immunosuppressant during inflammatory phase
	Aids in cell migration and fibronectin binding
	Augments production of tendon sheath fibroblasts, expression of type I and III collagen
	Improves tendon mechanics during healing
	Control of angiogenesis and fibrosis
PDGF	Role in the early phase of tendon damage
	Facilitates proliferation of other growth factors
	Attracts stem cells and white blood cells
	Stimulates angiogenesis
	Contributes to tissue remodeling
VEGF	Expression peaks after the inflammatory phase
	Promotes angiogenesis-neovascularization
b-FGF	Appears to stimulate angiogenesis
	Helps in regulation of cell migration
	Stimulates proliferation of capillary endothelial cells
	Influences fibroblasts to create collagenase
	Enhances angiogenesis
	Contributes to production of granulation tissue

IGF-1 = insulin-like growth factor; TGF-β = transforming growth factor-β; PDGF = platelet-derived growth factor; VEGF = vascular endothelial growth factor; b-FGF = basic fibroblast growth factor.

*Data from references 6, 9, 10, 12, 19, 46, 52, 102, and 103.

PRP

PRP is prepared by centrifuging autologous, anticoagulated whole blood. PRP is composed of 3-8 times the concentration of platelets contained in whole blood; therefore it contains a hyperphysiological content of autologous growth factors. Of note, a universally accepted definition of PRP in terms of concentration does not exist. The range of ideal concentrations is primarily based on opinion, and most publications differ on the PRP concentrations cited.

Citrate can be used to inhibit the clotting cascade by binding ionized calcium. Centrifugation separates the following: (1) the plasma (top layer) from (2) the platelets and white blood cells (buffy coat, middle layer) and (3) the red blood cells (bottom layer) because of differences in specific gravity. To further concentrate the preparation, a second centrifugation separates the PRP from platelet-poor plasma (PPP). Of note, the use of 2 spins versus 1 spin is controversial. Although a second spin will certainly concentrate the platelets

Figure 1. Platelet Concentrate System. Photo courtesy of Harvest Technologies, SmartPReP.

further, it remains a subject of discussion whether this step is necessary. The PRP (middle layer) is then drawn off, and the addition of calcium chloride or thrombin activates the PRP and results in the prompt release of 70% of the growth factors from the α granules within 10 minutes (and nearly all the contents within an hour). The issue of preactivation is also controversial, and not all clinicians include this step. The volume of PRP and concentration of platelets yielded from a volume of whole blood can differ based on the preparation system used [12,13,19,20]. For example, in our practice, we use the Harvest SmartPReP APC+ system (Harvest Technologies, Plymouth, MA) (Figure 1) and draw 20 mL of whole blood to generate 3 mL of PRP for small applications (with use of a small procedure pack), such as the elbow, foot, and ankle region. The larger procedure pack requires 60 mL of blood to be drawn and provides 7-10 mL of PRP for larger applications, including the hip and shoulder.

In 2008, Kajikawa et al [21] described the role of PRP in activating circulation-derived cells toward an injection site. It has been postulated that PRP can both inhibit excess inflammation and also augment stem cell proliferation and maturation, as demonstrated in in vitro studies. In the PRP studies that used tenocytes, PRP stimulated increased production of growth factors, such as vascular endothelial growth factor and hepatocyte growth factor. These growth factors generally help promote angiogenesis, which can contribute to tissue regeneration, tendon repair, and graft integration. The angiogenic factors can promote an increased blood supply to the injured area, which can facilitate delivery of circulating factors to aid the tissue remodeling [13,21-23]. Giusti et al [24] postulated that the most efficacious concentration of platelets to stimulate angiogenesis in vitro was 1.5×10^6 platelets/μL. In an adult, the normal platelet count is approximately 150,000-450,000 platelets/μL. PRP also has been found to induce type I collagen production and to provide support for cell binding [13,21,22]. Furthermore, the autocrine and paracrine functions of the growth factors help promote angiogenesis, extracellular matrix production, and collagen synthesis, which collectively influence tissue regeneration [8]. Further detailed basic science molecular functions of the specific growth factors are beyond the scope of this article.

PRP injections also involve a component of needle stimulus, which is speculated to induce focal bleeding and, as a result, can stimulate a biologic inflammatory response and promote repair in conjunction with the injected growth factors, which further recruit and activate circulation-derived cells [25].

The timing of regenerative PRP injections was studied in a rat model of patellar tendon injury. Chan et al [26] administered PRP injections to the tendon wounds on day 3 or day 7 after injury. Tendon segments were harvested on day 14, and the investigators found greater gains in mechanical properties (including peak loads) and maturation of healing tendons injected on day 7 in comparison with those injected on day 3, which suggests that the optimal time frame for injection of acute tendon injury may be just after completion of the inflammatory phase of the healing cascade, to augment the initiation and propagation of the proliferative phase. The authors agree with the limited data that support allowing the natural inflammatory phase to take place in acute soft tissue injury, including hemostasis and recruitment of inflammatory mediators. Further animal and human studies of PRP used in the treatment of both acute and chronic musculoskeletal pathology are discussed later in this article.

Differences Among Blood Products

Many variations of blood products have been evaluated in the literature. This article cites studies that analyzed several of these injectates; therefore, we offer a concise description of the various products below. Furthermore, within the realm of PRP, clinicians and investigators have differing protocols for producing PRP solutions. Centrifugation systems also produce varying products. Significant variability exists among PRP preparation systems, and, although, every company indicates that its system is the best, no clear comparative evidence is available to date. Moreover, some PRP protocols include white blood cells, some involve activation with thrombin or calcium, and the concentration of platelets can differ, depending on the system used. PRP combined with calcium chloride and/or thrombin can produce gels or fibrin matrices that can serve as scaffolds. A collagen platelet composite can be developed from PRP combined with a collagen mixture produced by using rat-tail tendons in an acidic enzyme solution that is subsequently neutralized [27]. Finally, gelatin hydrogels can be used with the PRP for a controlled-release mechanism [28].

Autologous conditioned serum is produced by incubating whole blood with glass beads to initiate monocyte activation and was developed by Orthogen AG (Duesseldorf, Germany). The product is a serum marketed as Orthokine and is rich in endogenous anti-inflammatory cytokines, including interleukins (IL-4, IL-10, IL-13), IL-1 receptor antagonist, and growth factors, including IGF-1, FGF-2, hepatocyte growth factor, and TGF-β1 [29,30]. To prepare the serum, whole blood is drawn into specialized syringes that contain glass beads, incubated for 6 hours, and then centrifuged. The serum is obtained and stored at −80°C until use [31].

Autologous plasma rich in growth factors is typically abbreviated as PRGF and often refers to use of the PRGF System II (BTI,Vitoria-Gasteiz, Spain). This process involves venous blood collection into 5-mL tubes that contain 3.8% trisodium citrate. These tubes are centrifuged at 1800 rpm for 8 minutes. The 0.25-1 mL fractions above the erythrocytes are obtained from the tubes and transferred to sterile tubes. Calcium can be added to the platelet-enriched plasma, which would result in the formation of a fibrin matrix that contains platelets [32,33].

In some studies, recombinant or isolated growth factors are evaluated, including insulin-like growth factor or PDGF, which should not be confused with PRP because it is just one of the growth factors that is released from the platelets [34].

Autologous conditioned plasma is prepared by using the Arthrex system (Karlsfeld/München, Germany), which uses a 15-mL double syringe [35]. Platelet-rich fibrin matrix is produced by using FIBRINET (Cascade Medical Enterprises, Wayne, NJ). Whole blood is centrifuged to obtain PRP, which is transferred into a glass bottle containing calcium chloride that is placed in a swing-out rotor centrifuge and produces a platelet-fibrin matrix that is a dense translucent yellow-white disk in appearance. Electron micrography reveals platelets within a fibrin network on one side [36].

The term "platelet concentrate" is often used in reference to isolated platelets without plasma that therefore would not clot [37]. However, at times it appears to be used synonymously with PRP. It has been used in conjunction with the PRP preparation system Biomet GPS II kit (Biomet, Warsaw, IN) [38].

Platelet leukocyte-rich gel is produced by centrifuging whole blood and obtaining the PRP and leukocyte-rich plasma, which then is mixed with a thrombin-calcium chloride preparation, and the gel form is produced. The nonactivated leukocytes in the formulation is thought to contribute antimicrobial properties [39].

PPP has been studied in comparison with PRP, and PRP has been found to be superior to PPP in efficacy [1,40]. PPP is produced after red blood cells are separated from leukocytes and platelets with further concentration by dividing the plasma into PRP and PPP.

Autologous blood injections (ABIs) involve whole venous blood that can be mixed with lidocaine or bupivacaine and then injected locally into the area of pathology. Because we do not presently perform ABI we cannot comment on the qualitative differences in outcome between PRP and ABI from our own experience. Results of recent studies have suggested that ABI in combination with dry needling may be an effective treatment for chronic lateral and medial epicondyle pain [41,42]. Other ABI studies are described in Table 2. Although the literature is building, evidence for both ABI and PRP are limited. However, the platelet concentration in PRP is significantly increased compared with that of whole blood [43]. Therefore, theoretically, the higher concentration of platelets taken from a larger volume of whole blood such as in PRP would be expected to be advantageous compared with ABI, because this is typically the "baseline" concentration of platelets and growth factors.

LITERATURE REVIEW: BASIC SCIENCE

In the basic science literature (Table 3), PRP has shown potential in stimulating bone regeneration. However, investigators differ in their views regarding thrombin activation. Gruber et al [44] found that platelets and thrombin-activated platelet products induced mitogenic activity of cultured human trabecular bone-derived cells and that platelet concentrates also enhance the proliferation of human osteoblast-like cells [45]. Interestingly, Han et al [16] found that PRP augmented the quantity of marrow stromal cells in a dose-dependent manner at 48 hours but that thrombin-activated PRP did not do so. When using a rat model, PRP appeared to amplify in vivo demineralized bone matrix osteoinductivity. Chondrogenesis was seen in 2 weeks and osteogenesis in 4+ weeks in the nonactivated PRP cohort. However, with thrombin activation, results were suboptimal and also yielded inflammatory cells that were not seen in the nonactivated group.

Osteoarthritis models also have been used to study the effects of PRP on synovial cell biology. Cells from 10 patients were cultured and exposed to either a platelet-poor or platelet-rich solution. The investigators found that the platelet-rich solution in growth factors enhanced hyaluronic acid secretion and concluded that intra-articular injections of platelet-released growth factor may be useful in joint homeostasis by contributing to hyaluronic acid restoration [46].

PRP also has been studied in the context of discogenic regeneration in hopes of finding a novel therapeutic option for back pain. Chen et al [47] found that administering PRP to human nucleus pulposus (NP) cells resulted in NP proliferation and differentiation, accelerated proteoglycan matrix accumulation, and decreased apoptotic cell numbers. Furthermore, PRP contributed to tissue engineering of NP by using type I and II collagen scaffolds, with resultant evidence of chondrogenesis.

Table 2. *Lateral epicondylitis studies*

Study (y)	Study Design	Human or Animal	Diagnosis	Intervention	Control Group	Details	Outcome Measures	Results
Mishra & Pavelko (2006) (53)	Prospective, cohort study	Human, nonsurgical	Lateral epicondylitis	PRP injection (N = 15)	Local anesthetic injections (N = 5)	Chronic, mean of 15 mo of pain, refractory, considering surgery	VAS	PRP group: 60% improvement in pain scores at 8 wk, 81% at 6 mo, & 93% at follow-up longer than 1 y out
Peerbooms et al (2010) (54)	Randomized controlled trial	Human, nonsurgical	Lateral epicondylitis	PRP injection (N = 51)	Corticosteroid injection (N = 49)	Chronic, more than 6 mo of pain; peppering technique was used	VAS, DASH score	73% success rate in the PRP group, 49% in the corticosteroid group; PRP group progressively improved; the steroid group regressed
Edwards & Calandruccio (2003) (55)	Prospective, case series	Human, nonsurgical	Lateral epicondylitis	ABIs (N = 28)	—	At least 3 mo, conservative management failed	VAS, Nirschl stage scores	1. 79% of the patients had significant or complete relief of pain even w/strenuous activity 2. Average pain and Nirschl stage scores decreased 3. 9 patients had additional injections and had greater improvement in Nirschl scores
Suresh et al (2006) (42)	Prospective, case series	Human, nonsurgical	Lateral epicondylitis	ABIs (N = 20)	—	Chronic, refractory, 12 mo symptomatic; dry needling was used	VAS scores, modified Nirschl scores, ultrasonography	1. Improved modified Nirschl scores 2. Significantly improved VAS scores 3. Decreased hypoechoic tendon changes on ultrasound at 10 mo
Connell et al (2006) (56)	Prospective, case series	Human, nonsurgical	Lateral epicondylitis	ABIs (N = 35)	—	Chronic, refractory (mean of 13.8 mo symptomatic)	VAS scores, Nirschl scores, ultrasonography	1. Significant improvement in VAS & Nirschl scores 2. Improvement in number of interstitial cleft formations, tendon thickness, & hypoechoic changes on ultrasonography
Gani et al (2007) (57)	Prospective, case series	Human, nonsurgical	Lateral epicondylitis	ABIs (N = 26)	—	Chronic, refractory (over 6 mo duration of symptoms)	VAS scores, Nirschl scores	1. 15 patients (58%) had complete relief of pain during strenuous activity 2. 5 patients (20%) had mild pain during strenuous activity & 6 patients had no change (of the 11 patients, 7 had previously received more than 3 local steroid injections without any relief)

PRP = platelet-rich plasma; VAS = visual analog pain score; DASH = Disabilities of the Arm, Shoulder, and Hand score; ABI = autologous blood injection.

Table 3. *Literature review: PRP basic science studies*

Substrate	Findings
Equine flexor digitorum superficialis tendon explants	Cultured in PRP & other blood products at various concentrations; PCR measurements found that TGF-β1 and PDGF-BB concentrations were highest in PRP; tendons cultured in 100% PRP had greater anabolic gene expression with no increase in catabolic gene expression (of MMP-3 & MMP-13) (104)
Human tenocytes	Both platelet-rich and platelet-poor clot releasates induced cell & collagen synthesis, but only the platelet-rich group had a mild increase in matrix-degrading enzymes (105)
Porcine-derived chondrocytes	Cultured in alginate beads and either 10% PRP, 10% platelet-poor plasma, or 10% fetal bovine serum; the PRP subset had higher DNA content, proteoglycan, & collagen biosynthesis; we suggest that PRP may have uses in cartilage tissue engineering through its potential to stimulate articular chondrocyte proliferation & matrix synthesis (106)
Mesenchymal stem cells	Inactivated, buffered PRP can augment mesenchymal stem cell proliferation & may influence chondrogenic differentiation (107)
Rabbit SMSC	Through immunofluorescence staining & PCR mechanisms, SMSCs were cultured in vitro; investigators found PRP enhanced osteogenic activity, differentiation of the SMSCs in a concentration-dependent manner (108); muscle-derived stem cells have high myogenic potential, which offers implications in musculoskeletal conditions, including w/innovative therapies such as gene therapy and tissue engineering (109,110)
Rat calvaria osteoblasts	Platelet-rich fibrin had a more gradual peak of growth factors & induced greater expression of alkaline phosphatase & mineralization of rat calvaria osteoblasts in vitro compared w/PRP (111)

PRP = platelet-rich plasma; PCR = polymerase chain reaction; SMSC = skeletal muscle-derived stem cell; TGF-β1 = transforming growth factor; PDGF-BB = platelet-derived growth factor composed of two BB chains; MMP = matrix metalloproteinases; DNA = deoxyribonucleic acid.

LITERATURE REVIEW: ANIMAL AND HUMAN STUDIES

Acute Muscle Tears and Muscle Strain Injuries

As previously described, recovery from muscle tissue injury involves inflammatory, proliferative, and remodeling phases. Secreted growth factors play a pertinent role in the healing cascade, and vascularity of the tissue is also an important determinant. Muscle repair and regeneration constitute a complex biologic process in which inflammatory cells are involved in both injury and repair via growth factors, chemokines, cytokines, and free radicals. After muscle injury, an inflammatory response takes place in which neutrophils and macrophages invade the area. Neutrophils express enzymes, such as matrix metalloproteinase-8, and may contribute to local muscle damage (neutrophils are extracted from PRGF preparations) [10,48].

It has been postulated that the TGF-β from platelet α granules may result in fibrotic healing, but this is speculation and has not been studied in the dynamic environment of muscle regeneration [12,49,50]. Moreover, when administering ABIs to normal tendons in an animal model, no abnormal fibrosis is formed [51]. Further studies are currently underway to explore the dynamic interactions intrinsic to muscle repair.

In a study of rats by using a control group, Hammond et al [1] demonstrated that PRP shortened the recovery time in a high-repetition, small-strain model. Other investigators creatively injected anti-growth factor neutralizing antibodies into acutely injured muscle of mice and found fewer surviving myofibers [52].

A case report documented pain relief and accelerated return to competitive training a week after serial PRGF injections (weekly for 3 weeks) in the treatment of an acute adductor longus rupture in a bodybuilder (Table 4) [32].

Tendon

In an animal study that used older rabbits, Taylor et al [51] concluded that injecting autologous blood into normal tendons appears to be safe. They injected 28 rabbits with ABIs administered to their left patella tendons, assessed the histology and mechanical properties at 6 and 12 weeks, and compared results with matched controls by using the contralateral tendons. At 12 weeks, the ABI-injected tendons were significantly stronger, with a 15% increase in tensile strength. No difference in histology was found compared with normal tendons, no damage was evident, and no change in stiffness occurred.

Lateral Epicondylitis. In 2006 Mishra and Pavelko [53] evaluated chronic refractory lateral epicondylosis; this article is one of the most cited articles in the PRP literature. It is one of the initial studies that showed potential for the use of PRP. In this prospective cohort study, subjects were identified who had significant persistent lateral elbow pain for longer than 3 months, despite physical therapy and other conservation care interventions. All the patients were considering surgery. This cohort of patients was given either a single percutaneous injection of PRP (active group, n = 15) or bupivacaine (control group, n = 5). Visual analog pain scores and Mayo elbow scores were evaluated at 2, 6, and a mean of 25 months, and all the patients showed reduction in pain

Table 4. *Muscle injury studies*

Study (y)	Study Design	Human or Animal	Diagnosis	Intervention	Control Group	Details	Outcome Measures	Results
Hammond et al. (2009) (1)	Controlled laboratory study	Rat model	Muscle strain	PRP injection	Platelet-poor plasma as sham treatment or no treatment	Tibialis anterior muscle was strained by either a large, single lengthening contraction ("large strain") or multiple smaller contractions ("small strain"), both resulting in loss of force	Peak isometric torque measured, muscle regeneration assessed histologically	1. PRP shortened the recovery time toward full contractile function in the high repetition, small strain model; the time to full recovery was found to decrease from 21-14 d in the PRP group 2. Investigators speculated that PRP growth factors stimulated and enhanced myogenesis, which is an important factor in recovery from high repetition strains
Lefaucheur et al (1996) (52)	Controlled laboratory study	Mouse model	Muscle injury	Anti-GF neutralizing antibody injection	—	Injected anti-GF neutralizing antibodies into acutely injured extensor digitorum longus muscles	Histologic assessment	1. Suboptimal healing after anti-GF was injected 2. bFGF neutralization was associated w/decreased capillary and macrophage quantity, but increased neutrophils & T-cells 3. Anti-IGF-1 & anti-TGF-β1 correlated w/a reduced number of surviving myofibers, but they had differing roles in altering the inflammatory environment

PRP = platelet-rich plasma; GF = growth factor; bFGF = basic fibroblast growth factor; IGF-1 = insulin growth factor; TGF-β1 = transforming growth factor.

compared with preinjection scores. The patients with PRP noted 60% improvement in their visual analog pain scores versus 16% improvement in control patients ($P = .001$) at 8 weeks. At the final follow-up, the patients treated with PRP reported a 93% reduction in pain. Importantly, no patients treated with PRP were worse after treatment, and no complications were noted in this study. However, technically this study was not a randomized prospective study. The control group may be considered a sample of convenience, and, because of the small study size, the control group could not be evaluated past the 8-week mark; 60% of the control subjects (3 of 5) withdrew or sought other treatments.

Peerbooms et al [54] conducted a recent double-blinded randomized controlled trial in The Netherlands that provides level I evidence in favor of the use of PRP injections in the management of chronic lateral epicondylosis when compared with corticosteroid injections. Patients who had refractory lateral epicondylosis for longer than 6 months were randomly assigned to receive either a corticosteroid injection (N = 49) or an autologous platelet concentrate injection (N = 51) through a peppering technique. The results showed that, according to both visual analog pain scores and Disabilities of the Arm, Shoulder, and Hand (DASH) Outcome Measure scores, the platelet concentration injection group had statistically significant improvement at 1 year compared with the corticosteroid injection group. The corticosteroid group was better initially and then their condition declined, whereas the PRP group progressively improved. Both randomized controlled trials (RCTs) show promising results in terms of pain scores, although higher-powered RCTs are necessary to further confirm results. Promising outcomes also are seen in several case series of epicondylitis when using ABIs [42,55-57] (Table 2).

Patellar Tendinopathy (Table 5). In an in vivo animal study by Lyras et al [4,58], the mechanical properties and histology of partially resected patellar tendons (central portion) of white rabbits were examined after application of PRP gel. The mechanical properties of the regenerated tendon in the PRP group were significantly improved in relation to the control group, specifically in the early phase (the first 2 weeks) of tendon healing. We found limited human clinical data for this diagnosis. To our knowledge, most human clinical data come from Filardo et al [25] and Kon et al [59]. The study by Filardo et al [25] is one of the only nonrandomized controlled trials that evaluated PRP as a treatment for refractory patellar tendinopathy. PRP injection used in tandem with physiotherapy that focused on eccentric strengthening was compared with a control of physiotherapy treatment alone. The intervention group received 3 serial PRP injections, 2 weeks apart, in conjunction with physical therapy, which is distinct from other studies that used single injections and relative rest. Outcome measures included sports activity (evaluated with use of the Tegner score), European Quality of Life Visual Analogue Scale (EQ VAS) score, pain level, complications, functional recovery, and patient satisfaction. Results were obtained at the end of treatment and at 6-month follow-up. The PRP group had significantly better improvement than did the control group in all measures, including pain and activity level. However,

Table 5. *Patellar tendinopathy studies*

Study (y)	Study Design	Human or Animal	Diagnosis	Intervention	Control Group	Details	Outcome Measures	Results
Filardo et al (2010) (25)	Prospective, nonrandomized, controlled trial	Human, nonsurgical	Chronic refractory patellar tendinopathy	PRP injections, 2 wk apart + PT (N = 15)	PT only (N = 16)	The PRP group had a longer duration of symptoms; 150 mL of venous blood was extracted to produce 20 mL of PRP; 5 mL was injected within 2 h, remaining aliquots were stored at −30°C and injected at 15-d intervals; the platelet concentration was 6 times higher than that in whole blood	Tegner, EQ VAS scores, pain level, complications, functional recovery, & patient satisfaction	1. PRP group improved in all measurement scores 2. PRP group further improved at 6-mo follow-up after physical therapy was incorporated 3. A higher improvement in sports activity was found in the PRP group
Kon et al (2009) (59)	Prospective, pilot study	Human, nonsurgical	Chronic patellar tendinosis	3 consecutive PRP injections (15 d apart) (N = 20)	—	Mean of 20.7 mo of pain	EQ VAS score, Tegner score	Complete or significant improvement in 70% of patients at 6 mo; 80% were satisfied with the results
James et al (2007) (41)	Prospective cohort study	Human, nonsurgical	Chronic patellar tendinosis	Autologous blood injection (N = 47)	—	Mean of 12.9 mo symptomatic	VISA, ultrasonography	1. Improved scores, reduction in interstitial tears, tendon thickness, & tendinosis area 2. Patients returned to sports after about 14 mo after treatment
Lyras et al (2009) (4)	Controlled animal study	Rabbit model	Patellar tendon defect	PRP treatment (N = 20)	Surgical defect with no PRP treatment (N = 20)	PRP gel administered on surgically induced patellar tendon mid-portion resections	Mechanical properties & histology of the regenerated tendon were assessed after 14 & 28 d	1. In the earlier phase, the PRP group had a 72% increase in force to failure, 39% increase in ultimate stress, & 53% increase in stiffness compared w/controls 2. There was no statistical difference in the later stage evaluation 3. In weekly histologic analyses, better healing was seen in the PRP group, w/ greater neovascularization in the first 2 wk & with more dense & mature tissue at wk 3
Kajikawa et al (2008) (21)	Controlled laboratory animal study	Chimeric rats	Patellar tendon injury	PRP injection	No PRP injection	Studied PRP in the activation of circulation-derived cells after patellar tendon injury in chimeric rats expressing a green fluorescent protein in the bone marrow and in circulating cells	Cellular quantification, measurement of immunoreactivity for types I & III collagen	1. At 3 & 7 d after injury, cell proliferation of circulation-derived cells was 2 times higher in the PRP group compared with a control group (no PRP) 2. Early phase: immunoreactivity of types I & III collagen was higher in the PRP group

PRP = platelet-rich plasma; PT = physical therapy; EQ VAS = European Quality of Life Visual Analog Scale; VISA = Victorian Institute of Sport Assessment scores.

this was a pilot study that did control for the potential effects of the injection itself.

Achilles Tendinopathy (Table 6). A recent block-randomized, double-blind, placebo-controlled trial by de Vos et al [60] that was conducted in the Netherlands showed no significant difference between PRP and saline solution–injected control groups with chronic mid portion Achilles tendinopathy. This well-designed study looked at 54 patients aged 18-70 years who met clinical criteria for Achilles tendinopathy, with symptoms for at least 2 months. Of note, patients were excluded if they had previous treatment with an eccentric strengthening program. The patients were stratified by activity level and randomly assigned to receive either 4 mL of PRP (n = 27) or 4 mL of isotonic saline solution (n = 27). The treating physician and the patient were blinded to the injection through use of a covering sheath over the syringe and hub of the needle. With ultrasound guidance through the use of color Doppler to target the region of tendon degeneration, PRP or saline solution was deposited into several sites in the mid substance of the tendon. After the first week after the injection, an exercise program was started in both groups that consisted of 1 week of stretching exercises and then a 12-week daily eccentric exercise program. No significant difference in improvement was noted at 6, 12, and 24 weeks follow-up between these 2 treatment groups according to the Victorian Institute of Sports Assessment-Achilles questionnaire score, which quantifies pain and activity levels. In addition, no significant difference was found in patient satisfaction, return to sports, and adherence to the eccentric exercises. Although the study was well designed, it had a small sample size, and the degree of abnormality of the tendinopathy is unclear. Investigators used 2 mL of bupivacaine for preinjection, which is somewhat of a large volume relative to the size of the tendon and PRP injectate, which raises the question of whether a dilutional effect may affect results. Recent studies have raised a concern regarding the use of certain anesthetics (most notably bupivacaine) and their potentially hindering effects on tenocyte proliferation and extracellular matrix production [61]. Whether this factor can affect the outcomes of PRP treatment warrants further study. The investigators buffered the PRP with 8.4% sodium bicarbonate. Optimal pH for PRP is an area that needs further research. Lastly, their study did show a notable trend, with 78% of the PRP group returning to a desired sport compared with 67% of the placebo group. It is important to point out that both arms improved appreciably. The control group received a treatment that has been known to be effective, that is, eccentric strengthening. Further discussion regarding the important questions raised by this study is presented in the Discussion section below.

We found only one small human case control study that involved PRP augmentation of surgical repair of Achilles tendon tears. PRP was used in both injection form and scaffold graft form, which showed promising results with range of motion, return to activity, and ultrasonographic findings. In this study, an anti-inflammatory medication was given in the postoperative period, which is different from other protocols in which nonsteroidal anti-inflammatory drugs (NSAIDs) were avoided in the immediate post-PRP period [10]. In animal models, PRP enhanced the mechanical properties of transected Achilles tendons, including enduring increased stress at failure [5].

Rotator Cuff Tears and Tendinopathy (Table 7). A few studies show good outcomes in pain and functional scores, including a pilot study by Randelli et al [62], who looked at arthroscopic rotator cuff repair augmented with PRP. However, this study did not have a control group. Several studies postulated that sustained-release vehicles for PRP would be ideal to target the regenerative healing phase [6,63].

Gulotta and Rodeo [6] proposed that intraoperative growth factor delivery should ideally be administered via a sustained-release vehicle. This method ensures that active growth factors will be released and be present at the time when they would be most effective, that is, during the regenerative healing phase, because the inflammatory response typically supersedes anabolic factors earlier in the healing process. Gamradt et al [63] used a platelet-rich fibrin matrix with sufficient density to maintain a suture for fastening a clot at the tendon-bone interface to augment rotator cuff repairs. The preliminary data demonstrated that active growth factors can be released for at least 7 days, and the investigators propose that this timed release can be pertinent to optimize the efficacy of PRP in the healing process.

However, prospective, randomized, level I evidenced research, including a study by Weber et al [64,65], has been unable to duplicate any of the benefits purported in augmenting rotator cuff repair with PRP. The investigators used platelet-rich fibrin matrix to supplement arthroscopic rotator cuff repair and did not find significant differences in structural integrity compared with the control group [65]. Similar negative results have been shown in prospective comparative studies with other PRP products used to augment this surgery [66,67]. In a prospective series of patients undergoing arthroscopic rotator cuff repairs, PRP supplementation at the repair site resulted in fewer re-tears (56%) compared with no PRP supplementation, but no difference was found in standard shoulder test scores [68].

Digital Tendon Pathology. Bosch et al [69] used ultrasonographic tissue characterization with computerized mathematical analysis to quantify regeneration during the phases of repair after treatment of equine digital superficial flexor tendon lesions with PRP or placebo. They found greater healing properties in the PRP group. Through computer analysis of the ultrasound images, the investigators found that more than 80% of the pixels in the images

Table 6. *Achilles tendinopathy studies*

Study (y)	Study Design	Human or Animal	Diagnosis	Intervention	Control Group	Details	Outcome Measures	Results
de Vos et al (2010) (60)	Stratified, block-randomized controlled trial	Human, nonsurgical	Chronic mid-portion Achilles tendinopathy	PRP injection	Saline solution injection	Treated with eccentric exercises & PRP injections or saline solution injections	VISA-A questionnaire	1. Both groups improved, & they did not find significant differences between the groups
Sanchez et al (2007) (10)	Case-control study	Human, surgical	Achilles tendon tear	PRGF (N = 6)	Conventional surgery	12 athletes had open suture repair after complete Achilles tendon tear; 6 athletes received a 4 mL calcified PRGF injected intraoperatively within the tendon fibers after suturing; platelet-rich fibrin matrix was used to cover the site before closure of the skin; retrospectively compared with a matched conventional surgery group; diclofenac was given in the postoperative period	Range of motion, functional recovery, complications, ultrasonography, laboratory analysis	1. Platelet-rich treatment & surgery: earlier recovery of range of motion (by about 4 wk); quicker return to training & light running (difference of about 7 wk); less increase in cross-sectional area of the PRGF tendons on ultrasound
Aspenberg & Virchenko (2004) (112)	Animal study	Rat model	Transected Achilles tendon	Platelet concentrate injection	—	PRP injected into rat transected Achilles tendons	Mechanical properties & histology	1. 30% increase in tendon callus strength and stiffness after 1 wk 2. At 3 wk: mechanical properties & histology: greater maturation of the callus
Virchenko & Aspenberg (2006) (5)	Controlled animal study	Rat model	Transected Achilles tendon	A. Platelet gel or PRP injection in the Botox group (Botox) injections into the calf muscles for unloading. B. Mechanically stimulated in activity cages (increased physical activity) C. ± platelet gel D. ± Botox group	A. Saline solution/ buffer control injections in the Botox group B. Ordinary cages C. ± Platelet gel D. ± Botox group	Effects of platelets on Achilles tendon regeneration in rats 3, 5, & 14 d after transection	Tensile testing	1. At 2 wk, Botox group had reduced mechanical properties; in the early phases (d 3 and 5), PRP appeared to improve their mechanical properties of force, stiffness, & area 2. Non-Botox group: PRP (gel & injection) increased stiffness & increased stress to failure 3. Mechanical stimulation in isolation also appeared to increase force, energy uptake, and area but had no synergistic effect with platelet treatment

PRP = platelet-rich plasma; PRGF = preparation rich in growth factors; VISA-A = Victorian Institute of Sports Assessment-Achilles.

Table 7. *Rotator cuff and/or shoulder studies*

Study (y)	Study Design	Human or Animal	Diagnosis	Intervention	Control Group	Details	Outcome Measures	Results
Everts et al (2008) (39)	Prospective randomized, controlled, double-blind study	Human, surgical	Stage II chronic shoulder impingement syndrome	Platelet-leukocyte gel injection (N = 20)	No injection (N = 20)	PLRP administered in open subacromial decompression surgery	American Shoulder and Elbow Surgeons scoring system of activities of daily living, joint instability, VAS, pain medications, & range of motion	1. Greater improvement in VAS & shoulder range of motion 2. Less postoperative pain medication usage 3. Earlier functional recovery of activities of daily living compared w/the control group
Randelli et al (2008) (62)	Pilot study without control group	Human, surgical	Rotator cuff tear (undergoing arthroscopic surgery)	Autologous PRP + autologous thrombin component after tear repair (N = 14)	—	Autologous PRP was administered during arthroscopic rotator cuff repair	VAS, functional scoring (UCLA & Constant scores)	Improvement in VAS & functional scores at 6-, 12-, and 24-mo follow-up

PLRP = platelet-leukocyte-rich plasma; VAS = visual analog pain score; PRP = platelet-rich plasma; UCLA = University of California, Los Angeles.

demonstrated correct tissue alignment in the PRP-treated group compared with only about 60% of the tissue area that revealed correct alignment in the placebo group.

Ligament

Medial Collateral Ligament Injury (Table 8). An animal study evaluated the effect of isolated growth factors on medial collateral ligament (MCL) injuries. The results showed stronger ligaments with improved biomechanical properties when an individual growth factor, in this case, recombinant human PDGF, was administered compared with control subjects [34]. PDGF is one of the growth factors involved in the healing process and one of the growth factors released from PRP.

Anecdotal evidence has demonstrated favorable outcomes in the management of acute MCL sprains in professional elite athletes when using PRP treatments. The media highlighted the case of a wide receiver for the Pittsburgh Steelers who had PRP treatment for an MCL sprain and was able to play in the Super Bowl 2 weeks after treatment [70]. This accelerated effect does not seem entirely consistent with the proposed action of PRP based on our current understanding. In our experience, we have found that some patients experience complete relief of pain within a few days after the injection, which is earlier than expected. We hypothesize that this effect may be associated with the release of the serotonin from the platelet-dense granules, which may have pain-modulating effects. However, given the short duration of release from the platelets and the short half-life of serotonin, the effect is unlikely to be sustained. Presently, the PRP literature is in its infancy, and further study is certainly warranted. In our limited experience with professional athletes with grade 2 and 3 MCL sprains treated within 1 week with PRP injection, the athletes were able to return to game play approximately 2 weeks before anticipated return to play with the given degree of ligament injury. However, currently, no level I

Table 8. *MCL studies*

Study (y)	Human or Animal	Diagnosis	Intervention	Control Group	Outcome Measures	Results
Letson & Dahners (1994) (34)	Rat model	MCL injury	Recombinant human PDGF injection (single growth factor); also compared w/combinations of growth factors (insulin-like growth factor type I & basic fibroblast growth factor)	Collagen emulsion without growth factor was injected into the contralateral injured knees as internal controls	Mechanical properties	1. PDGF group was 73% ± 55% stronger than their contralateral controls ($P < .0025$) w/increased stiffness & breaking energy 2. PDGF + other growth factor combinations: synergistic effects were not seen
Hildebrand et al (1998) (2)	Rabbit model	MCL injury	Growth factors by using a fibrin sealant delivery vehicle (fibrinogen & thrombin w/calcium & factor XIII)	Fibrin sealant only	Mechanical properties, histology	At 6 wk, biomechanical results & histology: improved ultimate loads, energy absorbed to failure, & final elongation values in the treatment group were 1.6, 2.4, & 1.6 times greater than values of the control group

MCL = medial collateral ligament; PDGF = platelet-derived growth factor.

clinical evidence exists to suggest that this treatment is efficacious for these conditions.

Anterior Cruciate Ligament (Table 9)

In a few RCTs, anterior cruciate ligament reconstructions supplemented with platelet-rich products consistently did not achieve any significant differences compared with control subjects [71-73]. When a collagen scaffold was used, PRP supplementation enhanced anterior cruciate ligament reconstructions, which resulted in improved biomechanical properties, with 76% greater yield at load ($P = .05$), 320% increase in linear stiffness ($P = .015$), and 47% decrease in the displacement at yield ($P = .05$) of the repair tissue at 3 months, as well as a significant increase in cell density [27]. The collagen scaffold was produced by solubilizing rat-tail tendons in an acidic enzyme solution, which is subsequently neutralized. After PRP is added, a collagen platelet composite is created, which was used in this study. This finding uncovers new therapeutic approaches to optimize the efficacy of PRP, namely the use of bioactive scaffolding and sustained-release vehicles. Congruent with this development, animal studies that used collagen-PRP scaffolds achieved superior results compared with studies that used PRP alone, which did not demonstrate improvement over contralateral, internal controls [27]. However, because these studies involved porcine and canine models, the outcomes cannot be directly extrapolated to humans.

Cartilage and Bone

Osteoarthritis and Articular Cartilage Defects (Table 10). No randomized controlled trials have been conducted in this area to date. We found an observational, retrospective clinical study that used hyaluronan as a control [74]. The investigators used serial intra-articular PRP injections with modest outcomes. The other clinical study was prospective and had more positive results but did not have a control group. Investigators found promising results in patients of younger ages, patients with a lower body mass index, males, and cases of milder severity [14].

A case report described a 12-year-old soccer player with knee pain and magnetic resonance imaging (MRI) findings of a large chondral lesion in his medial femoral condyle. He had a >2-cm loose chondral body in the intercondylar fossa and underwent PRP-supplemented arthroscopic surgery to reattach the loose body, with resultant good functional outcome [33].

In the animal literature, results of several studies demonstrated evidence of osteogenesis and formation of cartilaginous tissue with PRP combined with chondrocytes or a collagen matrix [75]. Sustained-release PRP intra-articular injections also resulted in increased cartilage matrix metabolism [3]. Although chondrocytes and PRP appeared to stimulate chondrogenesis subcutaneously, demineralized bone matrix and PRP did not stimulate osteogenesis intramuscularly [76,77], which prompts further questions about the substrates with which PRP may have synergistic effects and the environment in which the composite is placed. Intra-articularly injected sustained-release vehicles for PRP appeared to stimulate cartilage matrix metabolism, which suggests potential uses in osteoarthritis management [3]. In a canine model, a composite was created when PRP was combined with bone marrow stromal cells and demineralized bone matrix, then subsequently wrapped in a muscle flap that contained blood vessels. This combination appeared to enhance osteogenesis and vascularization [78].

In a study of porcine mandibular bone defects, PRP combined with bone marrow stimulated osteogenesis [40]. In another study, PRP was combined with bone graft and stimulated osteogenesis in rabbit calvarium defects [79]. Chondrogenesis was demonstrated in rabbit knee cartilage defects when PRP was used with a scaffold [80]. PRP alone also has been found to enhance the healing of diabetic fractures in rats [81].

Total Knee Arthroplasty. In 2 retrospective studies, patients with total knee arthroplasty (TKA) were either (1) treated with intraoperative platelet gels (PGs) [82] or (2) sprayed with activated PRP and then PPP at the wound site before wound closure [83]. The platelet groups generally had better postoperative hematologic status, better range of motion, and shorter hospital stays compared with the control group. In the first study, the platelet group also used a smaller amount of narcotic medications [82].

In another study, PG and fibrin sealants were administered intraoperatively, and similar results were achieved. Compared with a control group, the platelet group demonstrated higher postoperative hemoglobin levels, fewer blood transfusion requirements, shorter hospital stays, and decreased wound complications (eg, leakage or healing problems), with a P value of $<.001$ for these outcome measures [84].

Meniscal Pathology. The central region of the meniscus is avascular; therefore spontaneous reparative healing is unlikely, and definitive surgical management typically requires meniscectomy. The peripheral region is more vascular and therefore has a higher potential for healing. Spindler et al [85] found a dose-dependent response to an isolated growth factor (human, recombinant PDGF-AB was used) in sheep meniscal explants in the peripheral region but not in the central region. The function of PDGF is detailed in Table 1.

However, when sustained-release vehicles were used, PRP appeared to contribute to healing of the avascular (inner) portion of meniscal defects, as discovered in an in vivo study of rabbits when using PRP in controlled-release gelatin hydrogels (over 2-4 weeks). Ishida et al [28] prepared gelatin hydrogel by using chemical mechanisms that involved aqueous gelatin solution and glutaraldehyde. PRP was impreg-

Table 9. *ACL studies*

Study (y)	Study Design	Human or Animal	Diagnosis	Intervention	Control Group	Details	Outcome Measures	Results
Nin et al (2009) (113)	Prospective, randomized, controlled, double-blind study	Human, surgical	ACL tear	Platelet-enriched gel administered inside the graft & tibial tunnel (N = 50)	No gel (N = 50)	100 patients undergoing arthroscopic ACL reconstruction w/patellar tendon-bone allograft	Inflammatory parameters (C-reactive protein), MRI, VAS, International Knee Documentation Committee, & KT-1000 arthrometer measures	No significant difference in clinical outcome at 2 y
Orrego et al (2008) (38)	Single-blinded, prospectively randomized controlled study	Human, surgical	ACL tear	PC (N = 26), BP (N = 28), & a combination of PC & BP (N = 27)	No PC or BP (N = 27)	108 patients undergoing ACL reconstruction	MRI	1. At 6 mo, platelet concentrate had a positive effect on graft maturation in terms of MRI signal intensity (100% of patients versus 78% of the control group) 2. Platelet concentrate did not affect other MRI maturation criteria 3. At 3 mo, no differences were seen 4. Combining platelet concentrate with BP did not produce a synergistic effect
Silva & Sampaio (2009) (114)	Prospective randomized controlled study	Human, surgical	ACL tear	A. PRP in femoral tunnels at the end of surgery (N = 10) B. PRP in femoral tunnels at the end of surgery & intra-articularly at 2 & 4 wk after surgery (N = 10) D. PRP activated w/thrombin in the femoral tunnels (N = 10)	No PRP (N = 10)	40 patients undergoing ACL reconstruction w/ autologous hamstring tendons	MRI	No differences in MRI signal intensity at the fibrous interzone at 3 mo in the PRP & control groups
Joshi et al (2009) (27)	Controlled animal-laboratory study	Porcine model	ACL tear	CPC (with collagen produced from rat-tail tendons mixed with PRP) (N = 14)	No CPC (N = 13)	27 transected porcine ACLs, underwent suture repair	Mechanical testing, histologic analysis	1. At 3 mo, collagen-platelet group had greater mechanical properties of the ACL (higher yield load and linear stiffness) w/ncreased ligamentous cell density 2. Suggests that bioactive scaffolds can optimize the healing properties of PRP; of note, there was a period of relatively decreased mechanical strength at 6 wk in both groups, which coincided with a period of neovascularization, suggesting that structural protection may be indicated during this transitional period

Table 9. *Continued*

Study (y)	Study Design	Human or Animal	Diagnosis	Intervention	Control Group	Details	Outcome Measures	Results
Murray et al (2007) (73)	Controlled animal/ laboratory study	Porcine model	ACL tear	Suture repair augmented w/ collagen-PRP hydrogel	Contralateral side, similarly injured, suture repair alone	5 pigs w/bilateral ACL transections underwent repair	MRI & biomechanical testing	1. After 4 wk the PRP side had significant improvements in biomechanical properties, including load at yield, maximum load, & linear stiffness
Murray et al (2007) (72)	Controlled animal-laboratory study	Canine knee model	ACL tear	Collagen-PRP hydrogel	Contralateral side, similarly injured, untreated	Collagen-PRP hydrogel was administered to poorly healing ACLs	Histologic analysis	1. PRP-scaffold group had increased filling of the wound with repair tissue w/increased growth factors & proteins (fibrinogen, fibronectin, PDGF-A, TGF-β1, & FGF-2, & von Willebrand factor) 2. This was more similar to the regenerative environment seen in the healing process of extra-articular ligamentous injuries, which typically have better prognosis
Murray et al (2009) (71)	Controlled animal-laboratory study	Porcine model	ACL tear	Suture repair augmented w/PRP	Contralateral side, similarly injured, suture repair alone	6 pigs underwent bilateral repair	Anterior-posterior knee laxity & tensile properties	1. At 14 wk, knee laxity, maximum tensile load, & stiffness did not improve

ACL = anterior cruciate ligament; MRI = magnetic resonance imaging; VAS = visual analog pain score; PC = platelet concentrate; BP = bone plug; PRP = platelet-rich plasma; CPC = collagen-platelet composite; PDGF = platelet-derived growth factor; TGF = transforming growth factor; FGF = fibroblast growth factor.

Table 10. *Osteoarthritis, articular cartilage, bone studies*

Study (y)	Study Design	Human or Animal	Diagnosis	Intervention	Control Group	Details	Outcome Measures	Results
Kon et al (2010) (14)	Prospective cohort	Human, nonsurgical	Knee OA	PRP intra-articular injections administered (N = 115)	—	N/A	IKDC, objective & subjective, & EQ VAS	1. Notable improvement in IKDC & EQ VAS scores after PRP treatment 2. Remained positive at 6 mo follow-up 3. However, at 1-y follow-up, there was mild degradation of the scores, although they remained higher than baseline 4. Patients who were younger, male, had lower BMI, & less advanced osteoarthritis (on the Kellgren 0-IV scale) appeared to achieve better outcomes
Sanchez et al (2008) (74)	Observational, retrospective cohort study	Human, nonsurgical	Knee OA	3 weekly intra-articular injections of PRGF (N = 30)	Hyaluronan	N/A	WOMAC questionnaires	1. At wk 5, 33% of the PRGF group had improvement in WOMAC scores compared with 10% of the hyaluronan group
Sanchez et al (2003) (33)	Case report	Human, surgical	Chondral loose body	Knee arthroscopy reattached the fragment, supplemented with PRP	—	Adolescent soccer player with a large, >2 cm, loose chondral body (expected to have poor prognosis)	MRI, observed functional improvement, & return to activity	1. Improved articular cartilage healing & good functional outcome w/accelerated return to activity
Saito et al (200) (3)	Controlled animal study	Rabbit model	OA model	A. 3% PRP B. PRP in biodegradable gelatin hydrogel microspheres	A. 3% PPP	A. Rabbit chondrocytes were cultured in alginate beads. B. PRP in biodegradable gelatin hydrogel microspheres was injected intra-articularly into rabbit knees after ACL transection	Cartilage matrix gene expression, gross morphologic & histologic examinations	1. PRP appeared to stimulate chondrocyte GAG synthesis in vitro 2. Increased gene expression of proteoglycan core protein messenger RNA in the articular cartilage (ie, increased cartilage matrix metabolism) 3. Investigators postulated that these sustained-release injections may suppress progression of OA morphologically & histologically & therefore may have preventative implications in OA management

Table 10. *Continued*

Study (y)	Study Design	Human or Animal	Diagnosis	Intervention	Control Group	Details	Outcome Measures	Results
Wu et al (2007) (115)	Experimental animal study	Rabbit model	OA model	Chondrocytes + PRP composite injection (N = 4)	PRP only (N = 4)	N/A	Macroscopic examination, histologic analysis, glycosaminoglycan quantification, MRI	1. At 2 mo, hard masses were found subcutaneously in the chondrocyte-PRP group 2. MRI revealed cartilaginous tissue, which correlated w/ histologic findings & staining results (demonstrating proteoglycan & collagen in matrices) 3. Cartilage did not develop in the PRP-only group
Qi et al (2009) (75)	Controlled animal study	Rabbit model	Full-thickness cartilage defects in the patellar groove	PRP & bilayer collagen scaffold	Untreated or bilayer collagen scaffold without PRP	N/A	Repaired tissues were processed for histology & for mechanical test	1. PRP and collagen matrix induced the formation of cartilage tissues, showed enhanced repair of a larger surface area of the cartilage defects, & had higher GAGs content compared with collagen matrix alone or untreated controls
Gandhi et al (2006) (81)	Controlled animal study	Rat model	Diabetic fractures	Percutaneous PRP was administered to the fracture site	No PRP	Insulin-dependent diabetic fractures (impaired bone healing capacity) & nondiabetic fracture groups	Cellular analysis, mechanical properties	1. Early diabetic fracture callus: PRP had an effect on chondrogenesis, helping to normalize impairments 2. PRP-treated diabetic group later had improved mechanical properties of the fractured femur, including torque to failure & torsional rigidity compared with a non-PRP diabetic fracture group 3. However, their mechanical properties were inferior when compared with a non-diabetic fracture group
Ranly et al (2007) (76)	Experimental animal study	Mouse model	Osteoinduction model	Human-derived DBM + PRP implanted into the gastrocnemius muscle	—	8 immunocompromised mice; the DBM & PRP were obtained from different human donors	Histologic analysis, qualitative scores, & morphometric measurements	PRP did not appear to enhance or may even decrease the osteoinductivity of DBM; results were donor-dependent (different donors of the DBM or PRP)

Table 10. *Continued*

Study (y)	Study Design	Human or Animal	Diagnosis	Intervention	Control Group	Details	Outcome Measures	Results
Lopez-Lopez et al (2009) (40)	Controlled animal study	Porcine model	Mandibular bone defects	PRP at different concentrations, platelet-rich bone marrow, tricalcium phosphate	PPP & untreated controls	N/A	Electron microscopy analysis	1. Both PRP & bone marrow resulted in increased osteogenesis compared w/ controls 2. PPP was comparable w/controls
Nagata et al (2009) (79)	Controlled animal study	Rabbit model	Calvarium defects	Autogenous bone graft augmented with PRP	Bone graft or blood clot only	60 rabbits with calvarium defects	Histometric & histologic analyses	1. At 4 wks: PRP-graft group had greater bone formation than bone graft alone 2. At 12 wk, similar amounts of bone formation were seen in these 2 groups 3. Suggests that PRP may accelerate the healing of the bone graft sites & improve early healing
Sun et al (2010) (80)	Controlled animal study	Rabbit model	Articular cartilage defects of the femoropatellar groove	PRP + PLGA scaffold	Untreated lesions or PLGA administered alone	PLGA scaffold used	Macroscopic examination, micro-CT, & histologic evaluation	1. PRP + scaffold stimulated osteochondral formation with cartilaginous matrix & type II collagen accumulation: demonstrated in histologic analysis & micro-CT 2. Underlying subchondral trabecular bony ingrowth was seen 3. The other groups had little bone formation
Li et al (2009) (78)	Controlled animal study	Canine model	Tissue-engineered bone	BMSC + DBM + PRP − implanted into dogs	1. BMSC + DBM, but no PRP 2. Wrapped with a latissimus dorsi muscle flap versus with inferior fascia	The implants were wrapped w/either a latissimus dorsi muscle flap or inferior fascia	Radiographic evaluation, descriptive histologic analysis, & histologic quantitative analysis	1. Increased vascularization & osteogenesis of ectopic tissue-engineered bones w/ PRP versus with a non-PRP complex 2. Wrapping with the muscle flap (containing blood vessels) had better results

PRP = platelet-rich plasma; N/A = not applicable; IKDC = International Knee Documentation Committee; EQ VAS = European Quality of Life Visual Analog Scale; BMI = body mass index; PRGF = plasma rich in growth factors; WOMAC = Western Ontario and McMaster Universities Arthritis Index; MRI = magnetic resonance imaging; PPP = platelet-poor plasma; OA = osteoarthritis; ACL = anterior cruciate ligament; GAG = glycosaminoglycan; RNA = ribonucleic acid; PLGA = polylacticglycolic acid; micro-CT = micro-computed tomography; BMSC = bone marrow stromal cell; DBM = demineralized bone matrix.

nated onto the hydrogel, and it was designed to biodegrade the growth factors over an average of 2 weeks in in vivo conditions. Histology showed better reparative healing in the PRP group at 12 weeks compared with control subjects. As has been discovered from basic science research, PRP can promote neovascularity [23,43] and may play a role in reparative healing of avascular tissue. However, a constant supply of growth factors (extended-release or scaffolding) may be needed to provide sufficient vascular contributions to optimize healing.

High Tibial Osteotomy. Preliminary data from a randomized case-control study of high tibial osteotomy for genu varus demonstrated accelerated healing with neovascularization and deposition of new bone in a group of 5 patients who received lyophilized bone chips supplemented with PG when compared with a control group that had surgery without PG supplementation. The control group had evidence of fibrous tissue formation and histiocytic reactions in some cases [86].

In a prospective, randomized, controlled study, patients undergoing high tibial osteotomy had (1) implantation of PG, (2) PG and bone marrow stromal cells (BM), or (3) served as control subjects. At 6 weeks and at 1 year, greater osseointegration was seen in the PG and PG with BM groups. The investigators concluded that this therapy may enhance the osteogenetic potential of the bone chips [87].

Delayed Unions and Nonunions. In a case series without a control group, 32 patients with delayed union (at the tibia or fibula) or nonunions (at the humerus, femur, tibia, radius, fibula, or clavicle) were given platelet leukocyte–rich gel injections instead of open grafting procedures. Clinical examinations, radiographs, and dual-energy x-ray absorptiometry were used to monitor the patients. Union was successfully achieved in all subjects with delayed unions (average time to union was 9.3 weeks after the injection) and in 65% of the subjects with nonunions (average time to union was 10.3 weeks after the injection). In the remaining nonunion cases, generally more than 11 months had elapsed since the injury or the last surgery [88].

Intervertebral Disk. In a porcine disk degeneration model, PRP appeared to stimulate chondrogenesis. Increased chondrogenic matrix was found in the injected region, and the disk height index was also increased [89].

Spinal Fusion

A retrospective series of patients who had undergone lumbar spinal fusion with autologous growth factor concentrate used in conjunction with autograft demonstrated that union was achieved in all patients at a 13-month follow-up. This study used higher blood volumes and had the advantage of surgical equipment to prepare its PRP product. In this study, with use of a cell saver for pheresis, 450 mL of whole blood drawn from patients at the beginning of the surgery was used to produce a buffy coat concentrate of about 60 mL, which was then further concentrated to obtain the autologous growth factor concentrate, which resulted in approximately a 575% increase in platelet concentration (cells/mL) overall. The PPP and red blood cell layers were re-infused into the patient [90].

In a controlled cohort study, patients who sustained traumatic fractures of the lower thoracic or lumbar spine underwent spine stabilization surgeries and received a bone graft in conjunction with PRP or no PRP (control group). Minimal or no fusion was seen in 20% of the PRP group and 30% of the control group at follow-up, which suggests relatively faster fusion in the PRP group. The PRP group also had higher density values within the fusion mass, although similar visual analog scale pain scores were seen between the 2 groups [91].

Bone Lengthening. A retrospective study with a control group found that PRP and transplanted bone marrow-derived mesenchymal stem cells enhanced healing when transplanted during leg-lengthening procedures. The investigators propose that this combination may induce osteogenesis and vasculogenesis. Furthermore, they supported the notion that a proper environment with sufficient blood supply and a suitable soft-tissue environment is a crucial component in the success of PRP therapy [92].

OTHER CONDITIONS

Plantar Fasciitis

In a small case series, Barrett and Erredge [93] administered PRP injections to patients with recalcitrant plantar fasciitis. After 1 year, 7 of 9 patients had complete resolution of their pain. All the patients had ultrasonographic improvement, with reduction in thickness of the medial plantar fascial band and in the signal intensity of the fascial bands.

Peripheral Nerve Remyelination

In a rat model, repair of sciatic nerve transections with PRP augmentation of end-to-end neurorrhaphy resulted in improvements in latency time seen on nerve conduction studies and thicker myelin formation histologically in groups of rats sutured with 6 sutures supplemented with PRP compared with 6 sutures alone. The contralateral limbs also served as controls [94]. Shen et al [95] speculated that PRGFs may have neurotrophic or neuroprotective capabilities that may have therapeutic implications in brain or spinal cord injury, demyelinating diseases, cerebral ischemia, and neurodegenerative disorders.

DISCUSSION

Many animal and basic science studies during the past 2 decades have assessed the use and efficacy of PRP. Most of the studies we found were quite recent, within 2009 and 2010,

which reflects the new attention and focus that has steered the literature toward more studies of PRP. Many of these studies have shown the potential positive effect of PRP in the treatment of musculoskeletal conditions. However, there remains a paucity of human randomized controlled trials to provide level I evidence for the efficacy of this intervention. Most of the human studies reported in this article are case series or retrospective studies without a control group. Generally, they are small in size and lack power. Given the limited data, no clear definition of a standardized PRP treatment protocol has been established to date.

Investigators, including de Vos [60] and Peerbooms [54], have begun to address the utility of PRP with well-designed randomized controlled study protocols. However, these trials also have raised several important questions, some of which are discussed below. Generally, we have more unanswered questions than answered questions, and further research is certainly necessary.

- Does the amount of preinjection anesthetic affect outcomes?

Some clinicians hypothesize that use of a large amount on injectate can dilute out the PRP and cause migration of the pertinent growth factors away from the key site. The optimal amount of local anesthetic that should be used is presently unclear.

- Does buffering the PRP with sodium bicarbonate affect outcomes?

Some PRP protocols use buffering, but further research is needed to investigate the outcomes of these differing protocols. We use bicarbonate-buffered 1% lidocaine added in a small quantity to the PRP preparation to reduce the burning pain associated with the actual PRP injection. For example, 0.2 mL of buffered lidocaine will be added to 3 mL of PRP preparation. On the basis of preliminary evaluation, the effects of PRP are believed to be pH dependent, but the optimal pH is yet to be determined. Liu et al [96] found that the concentration of some platelet-derived growth factors and fibroblast proliferation were highest in a pH of 5.0 (although TGF-β was lower) when compared with higher pH levels. However, this is an area of active research. At the present time, standard PRP protocols do not buffer the PRP preparation.

- Does musculoskeletal ultrasound guidance improve results?

According to anecdotal experience, good outcomes have been achieved in clinics that use musculoskeletal ultrasound guidance to target the PRP toward critical anatomic structures. This practice certainly warrants further investigation.

- Are serial injections efficacious?

We are aware of practitioners who routinely perform a series of PRP injections at intervals of 2-4 weeks. As our experience with the procedure has grown during the past 2-3 years, we have not found this to be necessary. Wound healing is in an active state for at least 6 weeks, and remodeling occurs over months. We generally wait at least 6-8 weeks and often longer in the treatment of chronic conditions. As an example, in a recent study by Peerbooms et al [54], patients who underwent one session of an injection of PRP for chronic lateral epicondylitis continued to improve over 6-12 months.

- Is PRP more appropriate for some musculoskeletal conditions than for others?
- What are the relative benefits of PRP compared with ABI and other blood products?
- What is the optimal timing and optimal volume of PRP?
- What injection technique is most optimal (eg, layering or peppering)?
- What is the most optimal injectate concentration? (Four to 8 times normal platelet counts have been viewed as appropriate for PRP treatment. However, the optimal platelet concentration requires further clarification.)
- Does a patient's circulating platelet count have an impact on results? (Might there be a difference between high-normal versus low-normal platelet counts?)
- Can excessively high concentrations have adverse effects?
- A significant diversity is found among PRP preparation systems; is one superior to the others?
- What is the most optimal post-PRP rehabilitation program?

Regarding timing, we need to study whether PRP is beneficial for acute and/or chronic musculoskeletal conditions, and further evaluation is needed regarding which tissue injuries are most responsive to this treatment modality. The best evidence at present appears to be in treating chronic refractory enthesopathy in diagnoses such as chronic lateral epicondylosis and patellar tendinopathy. Few studies have evaluated acute pathologies. Thus far, to our knowledge, these are mostly case reports, case series, or anecdotal evidence in the media or in clinical practice that appear to reveal promising outcomes. However, currently there are no prospective RCTs that document faster recovery or a reduced re-injury rate in any acute sports-related injury. The use of PRP among professional athletes with acute musculotendinous and ligament injury is increasing exponentially, despite the paucity of robust scientific evidence. The potential decrease in time lost from play and related financial implications could be significant. Given the widespread ramifications for athletes at all levels, further research is clearly warranted in acute musculoskeletal injury. Research should focus on diagnosis-specific functional outcome measures and determination of time to return to previous activity level in elite and recreational athletes.

In 2010, the World Anti-Doping Agency (WADA) issued a statement regarding the use of platelet-derived preparations

stating that the preparations were prohibited if injected intramuscularly. Other routes of administration "require a declaration of use in compliance with the International Standard for Therapeutic Use Exemptions" [97]. In 2011, WADA removed platelet-derived preparations from the prohibited list "after consideration of the lack of current evidence concerning the use of these methods for purposes of performance enhancement. Current studies on platelet-derived preparations do not demonstrate a potential for performance enhancement beyond a potential therapeutic effect" [98]. WADA plans to monitor the ongoing research closely.

Therefore further research is essential for applications in sports medicine. If further positive level I evidence accumulates, PRP could potentially be covered by insurance plans in the future. Presently, PRP treatments are not reimbursed by most insurance coverage plans. The costs for the PRP kits are in the range of $140-$400, depending on the distributing company, the centrifuge system used, and the size of the kit (ie, the amount of PRP needed). PRP kits are disposable units used for each procedure and can include the sterile centrifuge containers, blood draw kits, and a number of syringes. When including facility fees and physician fees, costs of a PRP injection procedure can range between approximately $750-$2000. The wide discrepancy in costs is related to the difference in the costs of the various kits, systems, and fees. Nonetheless, generally, the costs of PRP injection procedures are more cost effective compared with the costs of surgery (potentially $10,000-$15,000) for several musculoskeletal conditions [70]. Therefore PRP injection may be an appealing alternative to surgical intervention from several vantage points.

Authors' Perspective

We need to confirm the most beneficial PRP protocols to optimize treatments for patient care, and we need further research to answer the questions that have not yet been addressed in the current literature. Respectfully, we offer our perspective, experience, and opinions regarding some of the questions that we raise below.

We have been using PRP for approximately 3 years. To date, we have performed >350 procedures. The more senior clinicians also have more than 3.5 years of experience with musculoskeletal ultrasound-guided interventions. Based on the limited data available at the time of this publication, in combination with our clinical experiences, we propose that PRP can be considered in the treatment of the pathologies mentioned below. However, because the scientific literature on PRP is still in its infancy, these suggestions should not be construed as the standard of care until further research can establish such standards. We can only comment on the experiences from our current practice and from the limited literature that had been summarized in this article.

- Chronic tendinopathies (some common examples are provided):
  - Elbow (lateral and medial epicondyle)
  - Shoulder (experience with rotator cuff tendons have been very favorable in patients with tendinosis without full-thickness tear or retraction)
  - Hip (especially gluteal, adductor, and proximal hamstring)
  - Knee (patellar tendon)
  - Foot/ankle (Achilles, peroneal, plantar fascia)
- Chronic pain and osteoarthritis
  - Knee (excellent outcomes if performed comprehensively, including treating intra- and periarticular structures; lower grades of arthritis without major deformity are most likely to respond; often of value after treatment with steroids or viscosupplementation no longer helps)
  - Ankle and foot
  - Shoulder (glenohumeral and acromioclavicular)
  - Hip
- Chronic ligamentous injury and pain
  - Ankle
  - Knee
  - Hip
  - Sacroiliac joint
- Muscle
  - Subacute and chronic symptomatic intrasubstance muscle tears

Patient selection criteria for PRP treatment that we use for the more common conditions are as follows:

Chronic tendinopathy (tendinosis and/or partial tear)

1. Pain duration >3-6 months
2. Symptoms and physical examination results consistent with tendinopathy
3. Recalcitrant to standard nonoperative treatment (physical therapy, NSAIDs, activity modification)
4. Tendinopathic changes on diagnostic imaging (tendinosis and/or partial tear): MRI and/or ultrasound evaluation
5. Patient wishes to pursue alternative to surgical debridement
6. No contraindications to the procedure exist (eg, infection, coagulopathy, or anticoagulants)

We generally use PRP for chronic injuries. An appropriate trial of rehabilitation will include a comprehensive approach with all phases or treatment: acute pain management, progressive restoration of flexibility, aerobic conditioning, strength, neuromuscular control, and sports-specific training (if possible). Eccentric strengthening is included for treatment of tendinopathy over a period of at least 6 months. Generally, we suggest initiating eccentric strength training approximately 2-3 weeks after PRP injection, that is, after the inflammatory stage of the healing cascade. However, at the present time, no data exist to support this time frame.

In addition, before performing PRP, imaging data such as MRI or musculoskeletal ultrasound should confirm and support the clinical impression. If diagnostic or therapeutic uncertainty remains, we will perform a diagnostic injection of the region with 1% lidocaine to see if it blocks the patient's musculoskeletal pain. From our experience, this procedure has been a good predictor of clinical success with PRP injection.

Acute myotendinous injury and/or ligamentous injury

1. Acute injury (7-10 days)
2. Symptoms and examination consistent with myotendinous injury at the enthesis, musculoskeletal junction, or muscle mid substance (strain or partial tear), or ligament injury (grade 1-2)
3. Partial tear documented on imaging (ultrasound or MRI)
4. No contraindications to the procedure (eg, infection, coagulopathy, or anticoagulants)

We have had the most experience in treating recreational and competitive athletes with chronic refractory tendinopathy and have had considerable success when using the aforementioned selection criteria. Our patients are categorized as having good or excellent outcomes based on their self-reported percentage of global improvement in pain level: 75%-100% improvement is deemed excellent and 50%-75% improvement is considered good. Diagnoses of lateral epicondylosis, patellar tendinopathy, rotator cuff tendinopathy, and knee osteoarthritis are among our most frequent indications and appear to have shown good to excellent outcomes in the short and long term. We will be publishing a case series with these data in the near future. Other common indications in our practice include hamstring tendinopathy, sacroiliac ligament enthesopathy, and gluteus medius tendinopathy, to name a few.

Whereas the aforementioned list is an outlined guide, our patients are managed on a case-by-case basis after thorough evaluation. Many factors are taken into consideration, including, for example, alternative treatments, sensitivity to (or intolerance of) medications, compliance with other treatments, and patient preference to avoid steroid injections.

We have limited experience treating acute injuries, but generally our outcomes average return to play 2-3 weeks before expected return with standard of care. Our most common indications include hamstring partial tear, medial collateral ligament sprain (grade 1-2), adductor longus partial tear, and gastrocnemius partial tear. Of note, not all acute injuries need to be managed with PRP. Professional athletes have been treated with PRP to presumably help expedite healing and return to play. At the current time, there does not appear to be enough evidence-based data to support or refute that practice. As previously stated, there is a paucity of literature relating to acute injury; this area of research demands further attention.

- What is the ideal time to administer PRP?

Currently we administer PRP for patients who have not responded to a comprehensive trial (3-6 months, typically closer to the 6-month duration) of standard management and rehabilitation for sports injury, are functionally impaired, and have a pain score that averages higher than 4 on a 0-10 visual analog scale. In addition, the athlete needs to have time to be out of play during the initial painful and postprocedure period. Our protocol averages return to sports at about 4 weeks for patients in these chronic cases (although it can range from 3 weeks to 3 months), but we manage each patient on an individual basis (see below activity progression for more details). Variables include the following: chronicity of symptoms, severity of the injury, other medical or orthopedic comorbidities, level and type of sports participation, and type and extent of injection performed. For acute injuries, we propose a time frame of administration at 7-10 days. This time frame is based on anecdotal experience and is supported by the animal model of patellar tendon injury reported by Chan et al [26], with better results seen with administration of PRP on day 7 compared with day 3 after injury. A person's return to the sport in acute cases is highly variable and is managed on a case by case basis, depending on the pathology, degree of injury, level of the athlete, and access to physical therapy and training facilities. The athlete's progress through the stages of rehabilitation and sports-specific training depends on his or her pain tolerance. The goal is to decrease recovery time for a specific injury by at least 2 weeks. The indications for patients in the subacute phase are not reviewed here because these patients are reviewed on a case-by-case basis, and a standardized approach has yet to be established.

- What is the ideal number of injections?

We do not have a routine number of injections. We begin with one injection. All injections are performed with musculoskeletal ultrasound guidance. We provide the patient with exercises and criteria for advancement. We have the patient return in approximately 6-8 weeks. If the improvement is 80% or greater as rated by the patient, then we defer further injections and continue to advance activity. If the improvement is less than 80% and the patient would like to achieve further gains, we would offer a second injection, if indicated, after reassessment. This decision is made entirely on an individual basis.

- What activities should be promoted or avoided during the intervals?

We find that activity progression and postprocedure pain is variable. There is typically a range of 2-10 days for the postprocedure pain to resolve. We initiate range of motion as tolerated immediately. We have the patient progress to light aerobic activity as tolerated, usually within 3-7 days. We have the patient progress to strengthening and sports-specific training in the 3- to 4-week time period, while recognizing this period is quite variable among athletes of different sports.

- What anatomic structures should be targeted, and how should they be targeted?

We routinely use musculoskeletal ultrasound guidance for injection. We approach the region, not just one point, depending on the clinical presentation. For example, athletes engaged in a jumping sport have a high incidence of anterior knee pain secondary to patella tendinopathy and/or enthesopathy. Target areas to treat may include abnormalities within the ligament and/or tendon or abnormalities at the entheses. Sonographic appearance, sonopalpation, and clinical correlation are all important. A peppering technique is preferred, with several needle passes through the tissues. We believe that it is important to target the local pathology but also to inspect and consider surrounding tissues as well, which may include the enthesis, peritendon, intratendinous, myotendinous junction, intramuscular, ligament, or intraarticular areas. In some cases we use color Doppler to target regions of neovascularity in tendinotic tissue. We have found, as results of studies suggest, that neovascularity generally correlates with tenderness on examination.

- Should NSAIDs, systemic steroids, or immunosuppressive medications be withheld? If so, for how long?

We advise patients to withhold NSAIDs for at least 10 days and preferably 3-6 weeks after a procedure. The reason that NSAIDs are withheld is empiric but not proven. NSAIDs inhibit the prostaglandin pathway and may reduce the beneficial effects stimulated by the release of growth factors from the delivered platelets by altering the cellular milieu necessary for the first phase (inflammatory) of the healing cascade. Theoretically, use of NSAIDS may impede or delay tissue healing and may even produce fibrosis [99-101]. However, there is no current clinical evidence in humans for this practice. We generally do not offer PRP treatment to patients who are taking systemic steroids or immunosuppressive agents, although we recognize that this may need to be considered on a case by case basis. We do not withhold low-dose aspirin that is used for cardiac prophylaxis.

- Are sustained-release vehicles, gels, and/or scaffolds more efficacious than isolated PRP injections?

Thus far, the literature has shown some efficacy when PRP is used in conjunction with sustained-release vehicles and scaffolds, as well as when combined with mesenchymal stem cells or fat grafts. However, presently, insufficient data exist to support or refute this finding. We do not have primary clinical experience with scaffolds or stem cell grafts, and this procedure is used only with specific clinical indications that are beyond the scope of this article.

- What are the return to play outcomes that may be achievable with PRP treatments, and is there a role for PRP in the management of acute injuries in professional athletes?

In our limited experience with professional athletes thus far, we have found that PRP treatments have enabled them to return to play 2-3 weeks earlier than expected. Return to play is an important factor in sports medicine, and it would be beneficial to further study the expected timeline to recovery in acute sports injuries.

- Is there a separate mechanism for pain modulation distinct from the tissue healing?

We also have found that some patients with chronic musculoskeletal conditions have experienced complete relief of pain within a few days after the injection, which is much earlier than expected. We postulate that this result may be associated with the release of the serotonin from the platelet-dense granules, which may have pain-modulating effects. However, given the short duration of release from the platelets and the short half-life of serotonin, the effect is unlikely to be sustained. Nonetheless, this hypothesis warrants further study.

CONCLUDING REMARKS

Recent advances in the published literature reflect the promise of PRP and regenerative biology in clinical practice. More recently, PRP has been studied in persons with chronic elbow tendinosis, plantar fasciitis, Achilles tendon repair, and augmentation of arthroscopic rotator cuff repairs, and anecdotal documentation has shown accelerated recovery in athletes who sustained muscular injuries. The regenerative properties of PRP also give it potential for use in the management of osteoarthritis and cartilage degeneration. In addition, it has been used to augment integration of surgical grafts to facilitate healing and anchoring. Further novel uses are undergoing studies, including the use of PRP-impregnated gelatin hydrogel microspheres to suppress the progression of intervertebral disk degeneration.

In this article, we have provided an in-depth review of the current literature. We acknowledge that, although the literature is building, it is still in its infancy and further randomized controlled trials that study the various clinical musculoskeletal conditions are needed, especially with higher numbers of subjects to increase power. Currently there is a scarcity of large-scale RCTs to provide level I evidence for PRP treatment in the management of musculoskeletal pathology. However, the existing literature is encouraging, and we are aware of several multicenter trials presently in progress that herald a promising outlook. Furthermore, our own patients' outcomes have been quite positive. We are currently reviewing our PRP outcome data. We anticipate that considerable research will emerge in the near future.

In conclusion, it is the our opinion that PRP and the field of regenerative bioinductive medicine hold significant promise in the ever-advancing field of sports medicine. Regenerative treatments may serve to fortify the arsenal of nonoperative management of sports injuries, as well as have a role as an

adjunct to improve postoperative healing. Significant developments certainly have occurred in regenerative biomedicine within the past 5 years, and we expect that further research on this topic will continue to shape the literature in the near future. It is also important to discuss costs. Although the exact cost of a PRP autograft procedure has yet to be determined, the value of this simple outpatient procedure is potentially high. We found that the cost of treating a single episode of tennis elbow with physical therapy to be at least $1200. In our practice, the total cost of tennis-elbow surgery, including fees for the surgeon, anesthesiologist, and facility, is between $12,000-$15,000. PRP has the potential to return patients to their activities of daily living, sports, and work without further medical economic intervention.

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