MANAGEMENT PERSPECTIVE

Optimization of ingredients, procedures and rehabilitation for platelet-rich plasma injections for chronic tendinopathy
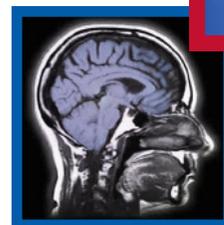
Kenneth Mautner[†1], Gerard Malanga[2] & Ricardo Colberg[1]

Practice Points

- There are many factors to consider in preparation and delivery of platelet-rich plasma (PRP) to obtain the optimum platelet product.

- Current evidence suggests that higher platelet counts with leukocytes and a slightly acidic pH injected under ultrasound guidance may be ideal to facilitate the healing of tendons following PRP injections.

- There is no consensus on rehabilitation after PRP injection, but a protocol that progressively increases the load and activity on a tendon which can augment the tissue healing cascade seems appropriate.

- Further research is needed in many areas pertaining to PRP to find the most effective ways to utilize this technology.

SUMMARY   There is considerable interest amongst clinicians and researchers to create the optimal platelet product to maximize outcomes with platelet-rich plasma (PRP) injections. PRP has been widely introduced as a safe alternative for treating tendinopathies. However, there is still limited clinical evidence describing the components of the platelet product and supporting its use in clinical trials. This article reviews the current literature regarding the role of PRP injections in the treatment of recalcitrant tendinopathies and the different factors in the platelet product that could affect the outcome, including the platelet count, presence of leukocytes, activators used, pH of solution and delivery method, among others. In addition, we address important concepts regarding rehabilitation after PRP procedures, which has little consensus to date and is the subject of much debate. Based on the phases of soft tissue healing, basic science research on platelets, as well as our clinical experience in treating over 500 patients with PRP, we will suggest guidelines regarding the optimal progression of rehabilitation and timing for return to previous activity following the procedure.

Historically, the treatment of tendinopathy, whether acute or chronic, has focused on treating perceived inflammation of a tendon and its surrounding sheath. These treatments have included anti-inflammatory medications, ice, and immobilization, usually followed by stretching and strengthening activities once pain had lessened. Often, those who were considered cured (because their pain lessened) found that, when they returned to sports, there was residual structural weakness of the involved tendon and often recurrent pain developed. This concept is illustrated in **Figure 1**.

Histological studies have revealed that these tendons are composed of degenerated collagen, fibrosis, neovessels and, most importantly, a

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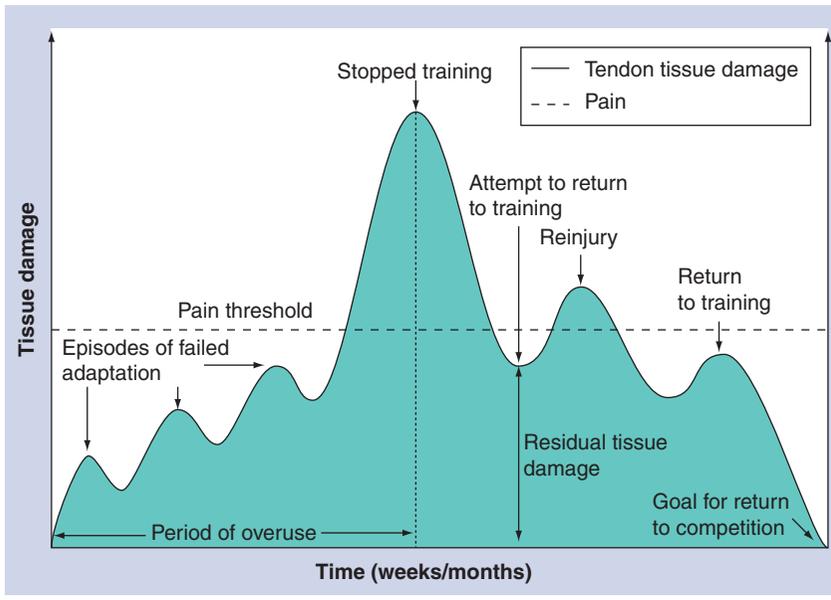[†]Author for correspondence: ken.mautner@emoryhealthcare.org

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Figure 1. Cell-matrix response in tendon injury.
Adapted with permission from [74].

lack of inflammatory cells [1,2]. This calls into question the use of anti-inflammatory agents in the treatment of these chronic tendon injuries. In the past, failed treatment protocols have included NSAIDs, corticosteroid injections, electrical stimulation, therapeutic ultrasound, phonophoresis and iontophoresis, as well as immobilization of the involved tendon. The scientific validity for these treatments is lacking [3–8]. While in the early stages of a tendon injury there is an inflammatory component [9], it is now understood that this inflammation is a necessary precursor to a cascade that should result in tissue healing. It therefore appears logical to prescribe therapies that can promote the healing of tendons, such as cross-frictional massage and soft tissue mobilization, as well as eccentric exercises to improve the tensile strength of tendons [10–12]. Despite these treatments, some tendons do not improve because the structural integrity of the tendon is not corrected [13]. This has led clinicians to employ biological products such as platelet-rich plasma (PRP) to augment the healing of chronically painful tendons that have failed traditional treatments [14–17].

Platelet-rich plasma has been defined as the supernatant obtained following low g-force centrifugation of a unit of whole blood, which produces a baseline platelet count [18]. The first clinical use of PRP in the USA was in 1987, to control wound healing after cardiac surgery [19]. Since that time, several fields of medicine

have used this technology, including dentistry, wound healing, ophthalmology, urology, maxillofacial surgery and cosmetic surgery, among others [14,15,17]. Over the last several years, there has been a significant increase in the use of this technology among musculoskeletal and sports medicine physicians. The theory is that growth factors released from the α-granules of platelets in supraphysiologic amounts can augment the natural healing response in one's own body [14,20]. In addition to growth factors, platelets also release many bioactive proteins, such as stromal-derived factor-1α, which are responsible for attracting mesenchymal stem cells, macrophages and fibroblasts that not only promote removal of degenerated and necrotic tissue, but also enhance tissue regeneration and healing [21,22].

Despite the widespread adoption of PRP in Sports Medicine clinics, there is still limited clinical evidence to support its use. At this time, there have been only six published research studies on humans that involve PRP injections to treat tendinopathy [23–28]. These studies (Table 1) contain such great diversity of methods with regards to the platelet product, procedure and rehabilitation after the procedure that it is difficult to make significant conclusions about their efficacy. More recently, one of those studies, a double-blind randomized controlled trial on chronic lateral epicondylitis, republished their results showing maintenance of improvement at a 2-year follow-up in the PRP treated arm [29]. Furthermore, the preliminary report of a multicenter retrospective satisfaction survey conducted on 180 patients with recalcitrant tendinopathy at least 6 months after PRP injection demonstrated that 82% of patients had moderate-to-complete resolution of their symptoms, with an 85% satisfaction rate and 75% reduction in VAS (from 7.0 to 1.8) [30]. It is also important to note that there have been no reported complications in the literature on patients treated with PRP, including a large prospective study on 808 patients treated for osteoarthritis of the knee [31].

There are multiple factors that influence the efficacy of each PRP injection procedure. These include, but are not limited to: platelet concentration, leukocyte count, pH of the injected substance, use of activators, the total number of injections given and the method of delivery (palpation of landmarks or with ultrasound guidance) [15,17,32]. Furthermore, following the

Table 1. Comparison of the six published research studies on humans that involve platelet-rich plasma injections to treat tendinopathy.

Author	Body part	Number of patients, number in control group	Volume (ml) + concentration of PRP	Activator	Buffering agent	Anesthetic	US guidance	Rehabilitation/RTP	Ref.
de Vos et al.	Achilles tendon	54, 27 control (saline)	4 ml	None	Sodium bicarbonate	Marcaine™	Yes	7 days protected activity, 7 days stretching; 12 weeks eccentric exercises RTP after 4 weeks if pain <3	[23]
Filardo et al.	Patella tendon	15	20 ml/3 tx 600%	10% CaCl	None	Did not specify	No	7 days protected activity, 7 days stretching; 12 weeks eccentric exercises RTP after 4 weeks if pain <3	[24]
Gaweda et al.	Achilles tendon	14	3 ml	None	None	Did not specify	Yes	PWB for 3 days, PROM ×2 weeks, AROM, stretching weeks 2–6, then full load active exercise	[25]
Kon et al.	Patella tendon	20	20 ml/3 tx 600%	10% CaCl	None	Did not specify	No	24 h limited mobility, rest between 1st and 2nd injection, stretching between 2nd and 3rd and after 3rd injection RTP allowed 1 month after 3rd injection (2 months after 1st injection)	[26]
Mishra et al.	Lateral epicondylitis	20, 5 control (bupivacaine)	5 ml 539%	None	Sodium bicarbonate	Marcaine	No	24 h limited mobility, rest between 1st and 2nd injection, stretching between 2nd and 3rd and after 3rd injection RTP allowed 1 month after 3rd injection (2 months after 1st injection)	[27]
Peerbooms et al.	Lateral epicondylitis	100, 49 control group (steroids)	3 ml	None	Sodium bicarbonate	Marcaine with epinephrine	No	24 h limited mobility, 2 weeks stretching, then eccentric exercises RTP after 4 weeks as symptoms allow	[28]

AROM: Active range of motion; PROM: Passive range of motion; PRP: Platelet-rich plasma; PWB: Partial weight bearing; RTP: Return to play; tx: Treatment.

procedure, a wide variety of post procedure recommendations and rehabilitation protocols have been used. These protocols likely have a direct effect on the outcome of the procedure, as it is known that tendon regeneration can take several months, or even up to a year to occur [27]. Important variables in rehabilitation requiring validation include the need for immobilization following the procedure and the best time to introduce strength training (especially eccentric exercises) as well as the specific parameters to allow return to athletic activities.

This article will examine the available scientific literature regarding the various factors that can affect the outcomes of PRP procedures and propose a rehabilitation program based on basic science research to maximize outcomes. These variables will require continued validation in future clinical trials, with the recent focus of treating chronic tendinopathies on regeneration of healthy tissue as the ultimate goal in restoring function to patients.

Optimization of the ingredients
■ Platelet concentration
When considering the optimum platelet product, the first factor to consider is determining the ideal platelet concentration to enhance tendon healing. Platelet counts vary based on an individual's own blood morphology as well as the time of day the sample is drawn [33]. Normal platelet counts in blood range from 150,000/µl to 350,000/µl. A simplistic definition of PRP is that the platelet count must be above baseline [34,35]. Most commercially available platelet-concentrating machines can be divided into lower platelet concentration (2–3× baseline) and higher concentration (5–9× baseline). There was early literature that suggested platelet concentrations of 2.5–3× baseline were ideal and above that, there was an inhibitory effect on healing [36–38]. However, several recent articles have produced different conclusions about ideal platelet count and challenged the initial theories. Giusti and coworkers prepared platelet concentrates between 300,000/µl and 7.5 million/µl and found the optimal platelet concentration for angiogenesis was 1.5 million/µl (5–7× baseline). Lower levels produced less angiogenesis and inhibition was not demonstrated until levels reached 2–3 million/µl (10× baseline) [39]. Furthermore, Haynesworth showed that accelerated wound healing required at least 4–5× baseline count as the quantity of mesenchymal stem cells produced went up exponentially from 2.5 to 5–10× baseline platelet count [40]. Recently, Kevy replicated the work of Giusti and found that the ideal platelet concentrate is 1.5 million/µl (5–7× baseline) and could be as high as 3 million/µl (10× baseline) [41]. Kevy concluded that "no stand alone PRP device can achieve platelet concentration whose releasate results in inhibition" [41]. These recent studies have demonstrated that higher platelet-concentrations are ideal to promote healing of soft tissue.

■ Leukocyte concentration
There has been considerable debate in the literature as to whether leukocytes inhibit or promote tendon healing. The machines that produce a lower concentration of platelets tend to filter out white blood cells (WBCs) while the higher concentrating machines have higher WBC concentrations. The argument against leukocytes in the PRP is that the inflammatory reaction that is produced from WBCs, specifically from neutrophils, can be detrimental to soft tissue healing **(Figure 2)** [42]. Neutrophils contain matrix metalloproteinases (MMPs), some of which have been shown to increase tissue damage when released into soft tissue *in vitro* [42–45].

It is also important to look at the composition of WBCs in commercial PRP preparations. The preparations that do not filter out WBCs contain predominantly mononuclear cells, lymphocytes and monocytes, as opposed to neutrophils [33]. **Table 2** demonstrates the average composition of leukocytes in PRP versus whole blood with a commercially available centrifugation unit run 20 times consecutively [41]. Note the significantly lower amount of granulocytes present in the PRP sample (65.22 vs 24.46%) as opposed to whole blood. Kevy states that the amount of granulocytes present in this data is not enough to cause a significant inflammatory reaction [41]. In addition, stem cells have been found to reside with mononuclear cells (monocytes and lymphocytes), so a higher percentage of these cells may result in higher stem cell counts [41]. A study comparing PRP to whole blood and platelet poor plasma reported that the PRP concentrate actually suppressed cytokine release and limited inflammation, thereby promoting tissue regeneration [46]. The combined evidence suggests that there is a beneficial effect of having leukocytes in the PRP mixture, especially when associated with higher platelet counts.

Optimization of the procedure
■ Activators

Another question with PRP procedures is whether to activate platelets prior to injecting them. There are three main substances that activate platelets: collagen, thrombin and calcium. These activators differ in their potency of activation, so this difference has to be considered in choosing between them. Thrombin is a much stronger activator than calcium, which is usually injected as calcium chloride, and calcium is a stronger activator than collagen. There are also synthetic activators on the market such as recombinant thrombin and synthetic peptides which may offer more of a sustained release of growth factors upon activation [47]. Proponents of using activators claim that growth factors contained within the α-granules of platelets are rapidly released upon activation, which could cause a more rapid, improved healing response [48,49]. Opponents of using activators suggest that natural activation via interaction with one's own collagen is better as it allows for a slower release of growth factors over time, more consistent with the body's own physiologic healing response [50]. The only human studies that used an activator were done on the patellar tendon with no control groups [24,26]. The outcomes were comparable to nonactivated PRP studies done on other body parts [23,25,27,28]. Therefore, no conclusions can be made regarding activating PRP prior to injection.

■ pH

There is disagreement regarding the optimum pH of a PRP solution and the effect of changes in pH on the release of growth factors and the healing potential of PRP. Most of the platelet-concentrating products use anticoagulant citrate dextrose as its anticoagulant which binds calcium and prevents the initiation of the coagulation cascade. However, citrate in the blood creates a slightly more acidic environment; therefore, some experts suggest buffering the pH back to a 'more physiologic state' with sodium bicarbonate prior to injecting [27].

Early studies looking at wound healing suggested that healing begins with a low, acidic pH, which then gradually shifts to a neutral and then alkaline pH [51,52]. Liu and coworkers exposed a platelet concentrate to three different pH's (5.1, 7.1 and 7.6) and showed that at the lowest pH there was an increase in platelet-derived growth factors, which are thought to be
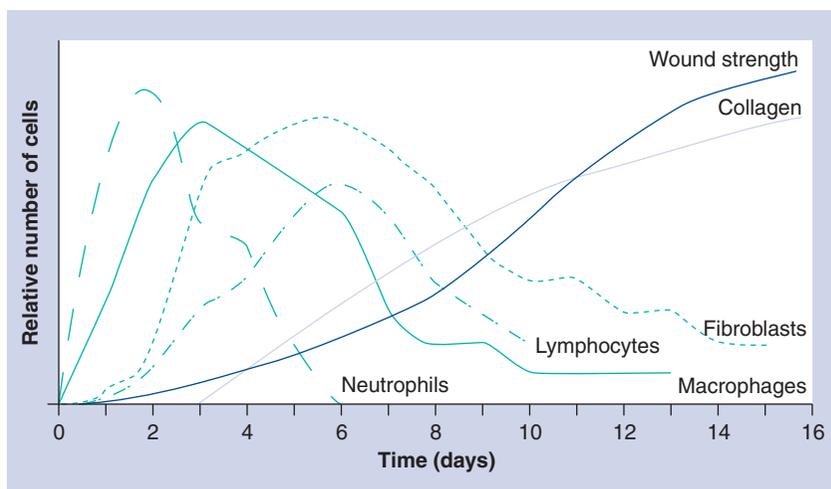

Figure 2. Leukocytes and wound healing.
Adapted with permission from [75].

active in early wound healing. However, in this study, the pH ultimately had no effect on collagen production [53]. Most studies have suggested that buffering PRP is not necessary and could, in fact, be detrimental to soft tissue healing.

Local anesthetics such as Xylocaine® or bupivacaine are often used during tendon injections and can also affect pH. These medications are acidic in nature and there has been debate as to whether it is safe to add them directly to PRP mixtures. Studies have demonstrated that adding local anesthetic to a wound has no negative effects on the healing of that wound [54]. Kevy looked specifically at Xylocaine mixed with PRP and found no negative effects on platelet function [41]. There is evidence to suggest that bupivacaine is more toxic to tenocytes than Xylocaine but the clinical effect with regard to tendon healing following PRP is not known [55].

■ Ultrasound guidance

It seems logical that when injecting a tendinopathic area, visualization of the damaged tissue via ultrasound guidance would facilitate direct

Table 2. Average composition of leukocytes in platelet-rich plasma versus whole blood with a commercially available centrifugation unit run 20 times consecutively.

	WBC × 10³/μl	Lymphocytes (%)	Monocytes (%)	Granulocytes (%)	WBC (% yield)
Whole blood	5.83 ± 0.77	26.91 ± 4.21	7.87 ± 1.43	65.22 ± 6.03	–
Platelet-rich plasma	21.09 ± 4.6	63.12 ± 9.71	12.42 ± 2.93	24.46 ± 9.23	43.1 ± 4.57

WBC: White blood cell.
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injection into this tissue. However, in the six human studies examining the efficacy of PRP only two of them used ultrasound to guide the procedure [23,25]. One of those studies showed no benefit over a control group in treating chronic achilles tendinopathy [23]. Preliminary results of a multicenter satisfaction survey on PRP with greater than 6 months follow-up demonstrates that using ultrasound guidance may improve outcomes [30]. In this study, lateral epicondyle PRP injections performed using ultrasound guidance have resulted in at least moderate improvement in over 90% of the cases and mostly-to-complete improvement in 83% of those treated. There is no literature comparing PRP injections performed with and without ultrasound guidance, but there are several studies, both randomized, controlled and on cadaveric specimens, which demonstrate improved accuracy of injection placement when using ultrasound guidance to inject into tendons, joints and other soft tissue structures [56–64].

Optimization of the rehabilitation program

There has been great variability, but little evidence, to guide clinicians in the rehabilitation period after PRP injections. The phases of tissue healing (Figure 3) following an injury can provide insight into what is occurring at a cellular level and can help guide the rehabilitation process.
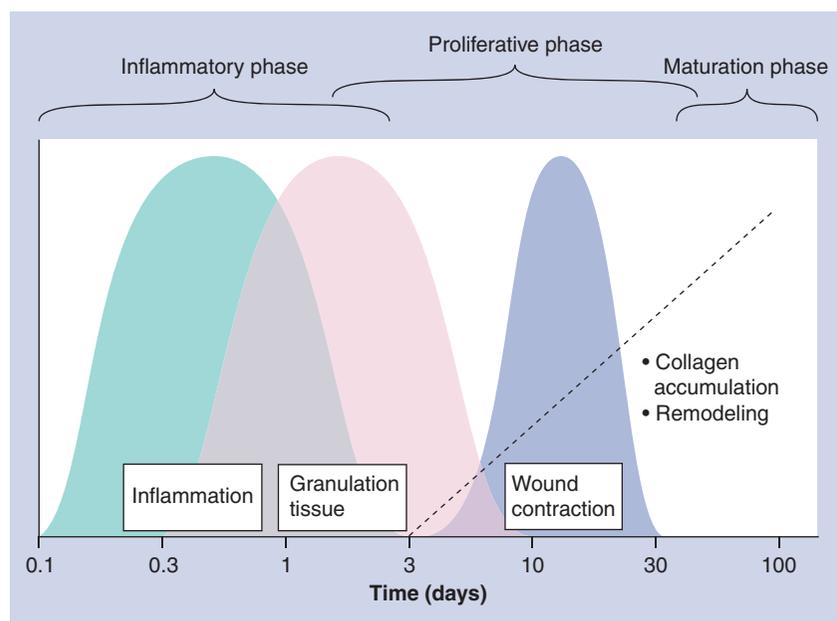

Figure 3. Phases of wound healing.
Adapted with permission from [76].

It is important to note that each phase is dependent on the preceding phase to work successfully. Phase I, the inflammatory phase, generally lasts 48–72 h. In this phase, debris is removed from the damaged tissue as cytokines and growth factors are recruited to assist in the healing process. Phase II is the proliferative phase, which generally lasts 48 h to 6 weeks. During this phase, there is proteolytic degradation of damaged tissue as well as attraction of neutrophils, lymphocytes and macrophages to the area. There is also introduction of fibroblasts, which form a new extracellular matrix that leads to wound contraction. There is increased neovascularization in the proliferative phase of wound healing, which recedes as phase III begins. Phase III is the maturation phase, when functional tissue is laid down [65]. It begins around the sixth week. During this phase, new extracellular matrix is laid down primarily through accumulation of type I collagen, the foundation of healthy tendons [32]. This phase lasts for several months, even up to a year. Thus, measuring outcomes from PRP injections should require adequate time for healing to occur.

Based on the framework above, the rehabilitation of PRP can be divided into three phases as well (Table 3). The first is the acute phase immediately after PRP is performed. The principal treatments of this phase are pain control and tissue protection. It is important to allow the inflammatory cascade to occur so minimal-to-no icing of the area and no anti-inflammatory medications are permitted. In addition, minimizing excessive motion of the involved area and allowing local platelet activation, while avoiding disruption of the fibrin plug, are important considerations. This can range from limiting weight bearing or resistance to frank immobilization. There are no studies to demonstrate that immobilization enhances outcomes and the negative effects of prolonged immobilization are well known [8].

After the acute inflammatory phase subsides, the next several weeks of rehabilitation should focus on preparing the body for new tendon formation during the proliferative phase. Controlled motion to the involved tendon is very important in the first two weeks after PRP treatment. Virchenko and Aspenberg demonstrated that if botox was administered to a muscle at the same time as PRP administration to the tendon, there was no platelet effect noted at the 14 day mark, as opposed to the control group with no botox. This study demonstrates that mechanical stimulation

Table 3. Suggested rehabilitation protocol following platelet-rich plasma injection.			
Phase	Length of time	Restrictions	Rehabilitation
Phase I: tissue protection	Days 0–3	Consider NWB or protected WB for lower extremity procedures, especially if in pain. No weight training, avoid NSAIDs and use limited ice	Relative rest. Activities as tolerated; avoiding excess loading or stress to treated area. Gentle AROM
Phase II: early tissue healing; facilitation of collagen deposition	Days 4–14	Progress to FWB without protective device. Avoid NSAIDs	Light activities to provide motion to tendon; aerobic exercise that avoids loading of the treated tendon. Gentle prolonged stretching. Begin treatment on kinetic chain/adjacent regions. Glutei strengthening and core strengthening
	Weeks 2–6	Avoid eccentric exercises. Avoid NSAIDs. Avoid ice	Progress to WB activities. Low weight, high repetition isometrics (pain scale <3/10). OKC activities. Soft tissue work to tendon with CFM, IASTM and 'dynamic' stretching
Phase III: collagen strengthening	Weeks 6–12	–	Eccentric exercises (keep pain scale <3/10). Two sets of 15 repetitions. CKC activities. Plyometrics; proprioceptive training and other sport-specific exercises. Progress to WB activities and consider return to sport if pain <3/10
	Months 3+	Reassess improvement; if not >75% improved consider repeat injection and return to Phase I	Progress back to functional sport-specific activities with increasing load on tendon as pain allows

AROM: Active range of motion; CFM: Cross-frictional massage; CKC: Closed kinetic chain; FWB: Full weight bearing; IASTM: Instrument-assisted soft tissue mobilization; NWB: Non-weight bearing; OKC: Open kinetic chain; WB: Weight bearing.

helps drive neo-tendon formation [66]. In conjunction with these results, there are several studies that look at mechanical transduction as a way to improve the tensile strength and healing of a tendon with or without PRP [67–69]. During the early rehabilitation program, gentle, prolonged stretching of the involved tendon is recommended. Preventing future overload on the tendon is imperative to avoid re-injury. Therefore, all patients who undergo lower extremity procedures will work on glutei (especially gluteus medius) strengthening, as many lower extremity injuries have been associated with weakness of the gluteus medius [70]. In general, from 2–6 weeks, we recommend soft tissue work to the involved tendon and beginning low intensity strengthening exercises, such as low weight, high repetition isotonic exercises, to progressively increase the load placed on the tendon.

The maturation phase begins around week 6. This is the time when eccentric exercises of the involved tendon are introduced. It is well known and validated that eccentric exercises are a proven treatment for chronic tendinopathy [12,67–69,71–73]. Alfredson has reported that one of the mechanisms for the positive effect of eccentric exercises on chronic tendon pain is by occluding and terminating neovessels, as the small nerves that accompany neovessels are thought to be a part of the pain generator in tendinopathy [72]. It is possible that early eccentric activity may cause a cessation of the regenerative cascade by not allowing proper angiogenesis to occur and putting too much load on the tendon too early. As healthy collagen begins to accumulate, the mechanical effects of heavier load exercises should improve the strength of the tendon. This theory needs validation through further research. Most human clinical trials on PRP allow progressive return to activities as symptoms decline. However, the available literature does not specifically address when those activities were resumed. Filardo and Kon reported an average return to activity for their successful treatments at 3 months, with continued improvements beyond 6 months [24,26]. Most of the research on PRP has shown that, on average, pain scores improve in a linear fashion over the first six months, but there is continued tissue healing and improvement in symptoms well beyond a year with a very low risk of recurrent injury during this time frame [29]. Nevertheless, there is a vast amount of additional research that is needed to help optimize healing after PRP injections.

Conclusion

Platelet-rich plasma injection is a promising new treatment for recalcitrant tendinopathy. As of now, the best indication for is for chronically

painful tendons that have failed to improve despite appropriate conservative treatments. When performing PRP, there are several variables to consider in optimizing the platelet product as well as the post procedure rehabilitation. Current research suggests that higher platelet counts with leukocytes and a slightly acidic pH injected under ultrasound guidance may be ideal to facilitate the healing of tendons following PRP injections. There continues to be a need to confirm this with clinical trials in the future. Also, there is still debate about which activators, if any, should be used and what is the optimal rehabilitation after PRP injections. The techniques and post-procedure protocols will be refined in the future as additional methods to treat recalcitrant tendinopathy in minimally invasive ways continue to evolve.

Future perspective

As with most new technologies and techniques, there has been an initial overexuberance and indiscriminant use of PRP. Although the basic science of platelet's healing properties has been elucidated, many of the specific issues that impact the efficacy of PRP treatment have not been defined. Foremost is the indication for the treatment, as proper selection for any procedure is paramount to enhancing outcome. In addition, the areas of controversy that we have delineated in this review need to be clarified: platelet concentration, leukocyte count, pH,

activation, method of delivery and, perhaps most importantly, a standardized post-procedure rehabilitation protocol. Finally, we are still learning about etiologies and risk factors for tendinopathy and need to keep in mind a holistic treatment approach so that things like vitamin deficiencies (e.g., vitamin D), hormonal imbalances, and functional deficits, to name a few, can be addressed as contributing factors to this painful condition.

The field of regenerative medicine is only in its infancy and as physicians worldwide continue to study cellular treatments for musculoskeletal conditions, new technology will continue to emerge. The future will include bone marrow aspirate, fat grafts and stem cell cultures, all of which are currently under investigation. It is our job, as scientists and clinicians, to learn the best way to apply these technologies and build evidence on the indications for these procedures so we make sure the 'hype' does not supersede the science.

Financial & competing interests disclosure

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■   of interest
■■   of considerable interest

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