

# Platelet-rich Plasma for Muscle Injury and Tendinopathy

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**Abstract:** Platelet-rich plasma (PRP) is increasingly used in Regenerative Medicine. The concept of PRP as a natural source of signaling molecules with paracrine effects in different cells is the basis for the increased PRP application as treatment for sports injuries. PRP recapitulates the principal functions of the natural healing response in orchestrating cell proliferation, differentiation, migration, and angiogenesis. After systematically searching the literature, we identified 21 trials for PRP injections in tendinopathy: 57% were uncontrolled trials and 1 cohort study in muscle. Leukocyte-PRP was used in 91.7% of tendons, of which 65.5% received 1 single injection. Given the lack of large controlled trials, it is clear that the effectiveness of conservative L-PRP treatments is not proven. The clinical evaluation of alternative formulations can be extremely informative. Other unexplored issues include activation, redosing, and concomitant longitudinal tenotomies. Limiting factors for the acceptance of PRP are the lack of evidence of obvious clinical improvement and reimbursement.

**Key Words:** platelet-rich plasma (PRP), tissue regeneration, muscle injury, tendinopathy, clinical trials

(*Sports Med Arthrosc Rev* 2013;21:191–198)

Participation in sport and leisure activities is widespread. Sports and physical activities of almost any kind are beneficial for the individual as well as for society as a whole in health promotion and the prevention of many conditions such as osteoporosis, cardiovascular diseases and diabetes, and improving mental health. However, sports injuries cost society billions of dollars in both direct and indirect costs.<sup>1</sup> Regenerative Medicine technologies such as PRP and stem cell therapies hold the promise of improved outcomes for musculoskeletal diseases and conditions for which there are currently limited or no treatment options. For instance, PRP injections have gained popularity among orthopedist and sports physicians in treating tendinopathies and muscle injuries; accordingly the global market for PRP valued at \$4.5 million in 2009 is ventured to be worth > \$120 million by 2016.<sup>2</sup>

The concept of PRP therapy as a natural source of signaling molecules with paracrine effects in different cells is the basis of PRP application in different tissues and clinical conditions. The ability to manipulate tissue repair using this safe strategy has led to much excitement and research efforts to elucidate the participation of PRP in repair mechanisms as well as the clinical potential of PRP therapies.<sup>3–5</sup> Concurrently, the application of musculoskeletal

ultrasound (US) has been expanding over the last decade and has demonstrated promise with regard to its current applicability in diagnostic, prognostic, and PRP delivery with direct visualization in tendinopathy and muscle injuries. US-guided PRP administration may be cost-effective especially when applied in patients with tendinopathy that do not respond to conventional management and had reached the surgical threshold.

The rise of such stimulating therapies to treat tendon and muscle problems compels us to refine our knowledge of PRP biology aimed at controlling the healing environment and improving clinical applications.<sup>6</sup> Thus, we first summarize recent information on the mechanisms inherent to PRP biology. We then describe factors that can influence the effectiveness of the various PRP formulations and stress whether this knowledge should be further explored for clinical benefit. Finally, we summarize data regarding the various PRP formulations and procedures used in tendinopathy and muscle injuries and the ensuing clinical outcomes.

## CLINICAL DATA: CONSERVATIVE TREATMENT OF TENDINOPATHY AND MUSCLE INJURIES WITH PRP

We conducted a systematic literature search using the databases of PubMed, EMBASE, Web of Knowledge from 1980 to present (December week 1, 2012) and Google Scholar. The following key terms were used in differing combinations: first, in terms of treatment, we searched using all current names that describe this therapy modality, that is, platelet-rich plasma (PRP), platelet-rich fibrin matrix, autologous fibrin, autologous conditioned serum, platelet concentrate, autologous growth factors, and plasma or preparation rich in growth factors; second, we searched for the target, using the following terms: skeletal muscle injury, strain and contusion or tendon injury, tendinopathy, tendinosis, tendinitis.

Only original clinical studies describing the conservative management of tendinopathy and muscle injuries with PRP injections are included. Case reports and surgical trials were excluded. From the included studies, the following data were extracted: study design, patient population, anatomic location of the injury, and outcome results, with special emphasis on PRP formulation and treatment aspects. We examined manuscripts to ascertain whether there is already more effectiveness for 1 PRP product/procedure over another (Fig. 1).

Important to this approach will be forthcoming studies, thus we gave a future insight by searching for imminent studies registered in the publicly available database ClinicalTrials.gov.

## Tendon Injections

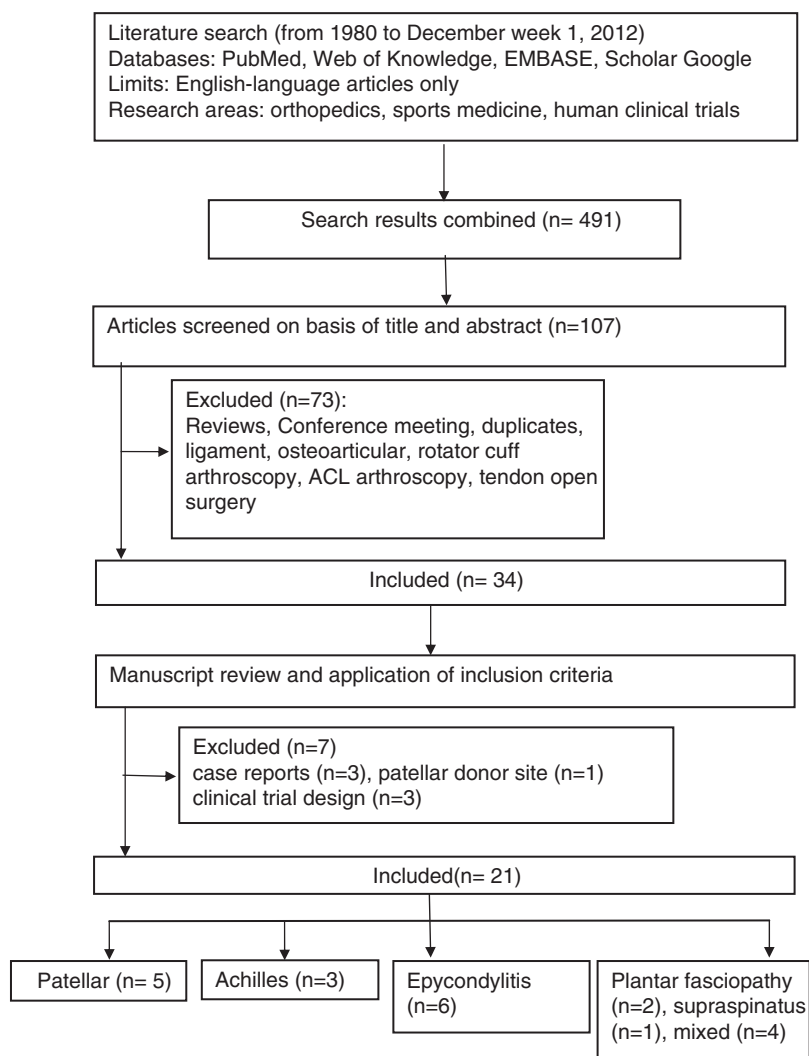
Currently, 21 published studies evaluate the efficacy of PRP injections in the management of tendinopathy, of which 57% (12 studies) were noncontrolled trials (Table 1). The sample sizes in the studies ranged from 6 to 80 cases,

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Disclosure: The authors declare no conflict of interest.

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**FIGURE 1.** Flow diagram of study selection.

and the duration of follow-up varied from 6 weeks to 2 years. The efficacy of PRP was examined for different anatomic locations; overall 553 tendons were treated, mainly 21.51% patellar tendons (119 cases), 22.78% Achilles (126 cases), 39.78% epicondylitis (220 cases), 11.39% plantar fasciopathy (63 cases), 2.89% supraspinatus (16 cases), and 1.62% others (9 cases). The primary outcome measure of concern was assessment of pain, and both pain reduction and improvement in function were the focus in the majority of studies.

### Patellar Tendinopathy

Five studies,<sup>7–11</sup> have examined the efficacy of PRP for patellar tendinopathy, and 2 other studies<sup>12,13</sup> examined together Achilles and patellar tendinopathies. The quality of the available evidence is very low: all but 1<sup>9</sup> were uncontrolled studies. A significant clinical improvement in both pain and function lasting about 6 to 9 months was reported in all noncontrolled studies. In contrast, the sole controlled study<sup>9</sup> showed no between group differences in pain, but the functional improvement (Tegner score) was higher in the PRP group.<sup>9</sup> As regards changes in tendon

structure, noncontrolled studies report a reduction in tendon irregularities [magnetic resonance imaging (MRI) assessment]<sup>13</sup> and also reduction of hypoechoic areas.<sup>12</sup>

An active clinical study is examining the effect of PRP in acute and chronic patellar tendinopathy (NCT0140682) by comparing US-guided PRP injection versus US-guided dry needling.

### Achilles Tendinopathy

One randomized clinical trial (RCT)<sup>13,14</sup> and 5 prospective case series,<sup>12,13,16–18</sup> 3 of which involved tendons in various locations,<sup>12,13,17</sup> have evaluated the efficacy of PRP injections in the Achilles tendinopathy; all but 2 (distal) case series dealt with tendinopathy of the main body of the tendon. Most tendons (81%) were managed with a single injection of 3 to 4 mL of L-PRP (platelet enrichment 4 to 8×). Of note, in a case series of patients with Achilles tendinopathy recalcitrant to conservative treatments, 2 US-guided injections and extensive scarifications was effective in reducing pain, enhancing function, and improving the structure of the tendon as assessed by US.<sup>12</sup>

**TABLE 1.** Conservative Management of Tendinopathy: Technical Characteristics of the PRP Product and Administration Procedure

References	Study Design, N/Follow-up	Patient Population	PRP Product and Procedure	Outcome Instruments/Results
Van ArK et al <sup>7</sup>	Patellar/case series, N = 5 patients, 6 cases/6 mo	Athletes, symptoms for over 12 mo VISA-P < 80, US hypoechoogenicity, recalcitrant to at least 12 wk eccentric training	P-PRP Plt: 1.7 × (ACP, Arthrex) single US-guided injection + physical therapy	VISA-P, VAS during daily activities, functional test/ 5/6 tendons showed an improvement of at least 30 points on the VISA-P after 6 mo
Gosens et al <sup>8</sup>	Patellar/case series N = 36, subgroups: refractory N = 14 vs. nonrefractory N = 22/ 18 mo	Resistant to conservative and surgical treatment N = 14, resistant but no injections, no responders to eccentric in any group	3 mL L-PRP (Plt: 4-8 ×; WBC: 6 ×), buffered pH: 7.4 + bupivacaine/no activation single blind injection/1 skin portal and 5 penetrations of the tendon	VISA-P, ADL, EVA/ clinical improvement in refractory and nonrefractory patients, better results in the last group
Filardo et al <sup>9</sup>	Patellar/cohort, PRP, N = 15 vs. physiotherapy N = 16 (matched for age, sex and sport level)/6 mo	Chronicity > 3 mo and recalcitrant to conservative and surgical treatment only in PRP the group	Blood bank: 5 mL L-PRP (Plt: 6 ×; WBC?) activated Ca <sup>2+</sup> mEq/dose 3 blind injections/biweekly + physical therapy	EQ-VAS, Tegner score/no significant improvement in PRP group for EQ-VAS and pain level; in PRP group, significant improvement in PRP group for Tegner score (+ 39 vs. 20%)
Kon et al <sup>10</sup>	Patellar/case series, N = 20/6 mo	Male athletes, consecutive cases, chronicity (3-60 mo). 8 patients recalcitrant to conservative treatment and 5 recalcitrant to conservative and surgical	Blood bank: L-PRP (Plt: 6 ×; WBC?) CaCl <sub>2</sub> -activated 3 blind injections/5 mL biweekly	EQ-VAS, SF-36 Tegner/ improvement in EQ-VAS, SF-36 and Tegner (sport return); 80% of patients were satisfied with treatment
Volpi et al <sup>11</sup>	Patellar/case series N = 8/4 mo	Young athletes, third proximal recalcitrant tendinopathy since at least 1 y	3 mL L-PRP (Plt: 4-8 ×; WBC: 6 ×) buffered pH: 7.4 GP/no activation + rehabilitation single blind injection	VISA-P, MRI/improvement in VISA (91%); reduction in irregularity in 80% of treated tendons (MRI, 4 mo)
Ferrero et al <sup>12</sup>	Achilles (n = 30) + patellar (n = 28) case series, N = 58/ 6 mo	Competitive and recreational athletes, resistant to conservative treatments	Blood bank: 6 mL L-PRP Plt: 5 ×; WBC: 6 ×/ thrombin activation US-guided/2 scarifications and 2 injections (3-wk interval)	VISA-P,-A, US/ improvement at 6 mo (VISA-P and VISA-A) reduction in hypoechoic areas and tendon thickness after 6 mo. Intratendinous vascularity increased at 20 d and 6 mo
Volpi et al <sup>13</sup>	Patellar (n = 13 tendons), Achilles (n = 4 tendons) 1 epicondylitis, 1 quadriceps. Case series N = 15 athletes 19 tendons/24 mo	All recalcitrant tendinopathy since at least 1 y. Patellar 9 young athletes the others recreational	3 mL L-PRP (Plt: 4-8 ×; WBC: 6 ×) buffered pH: 7.4 no activation, GPS and rehabilitation single US-guided injection	Improvement in VISA (+ 37) and reductions in abnormalities in 80% of treated tendons (MRI). The improvement of clinical symptoms is maintained for at least 2 y following treatment. Improvement less marked in Achilles
Monto <sup>16</sup>	Achilles/case series, N = 36 patients/24 mo		PRP single US-guided injection	The average AOFAS score increased from 34 (range, 20 to 60) to 92 (range, 87 to 100) by 3 mo after PRP treatment and remained elevated at 88 (range, 76 to 100) at 24 mo posttreatment
Gaweda et al <sup>17</sup>	Achilles/case series, N = 14 patients, 15 tendons/18 mo	All patients seeking treatment, exclude systemic inflammation	3 mL L-PRP (Plt: 5.5 ×; WBC: 6 ×) (Curasan) single US-guided injection into hypoechoic areas	AOFAS, VISA, 6wk, 3 mo, 6 mo, and 18 mo/ significant improvement in AOFAS (+ 41) and VISA (+ 72); reduction of tendon thickness and hypoechoic areas (US). Improvement in qualitative gray-scale US characteristics

TABLE 1. (continued)

References	Study Design, N/Follow-up	Patient Population	PRP Product and Procedure	Outcome Instruments/Results
de Vos et al, <sup>14</sup> de Jonge et al <sup>15</sup>	Achilles midportion/RCT PRP N = 27 vs. saline N = 27/6 mo (de Vos) 12 mo (de Jonge)	Minimal duration of symptoms 2 mo, excluded if previous full eccentric program or PRP	4 mL L-PRP (Plt: 4-8 ×; WBC: 6 ×) buffered pH: 7.4 no activation and eccentric exercises single US-guided injection	No differences in VISA and ultrasonographic improvement; 59% of patients were satisfied in both groups
Chaudhury et al <sup>26</sup>	Epicondylitis/case series N = 6/6 mo	US diagnosis extensor tendinosis, partial tera extensor < 50%	3 mL L-PRP 4 × Plt, 4 ×; WBC (Harvest SmartPrep) single US-guided injection	Contrast US: QLAB software(quantitative), MVI, microvascular imaging, 1 mo and 6 mo/ improved extensor tendon morphology
Creaney et al <sup>20</sup>	Epicondylitis/RCT PRP N = 80 vs. blood N = 70/1/6 mo	Resistant patients, PRTEE: 49	1.5 mL L-PRP (Plt: 2.8 ×) single spinning, buffy coat monthly US-guided injections (2) into clefts of hypoechogenicity (no dry needling)	PRTEE/improvement in both groups at 6 mo but no difference between groups. Higher proportion of failures (removed for surgery) in ABI, 12/17 vs. 7/24 in PRP. Success rate (50% improvement) at 6 mo: 66% PRP vs. 72% ABI
Peerbooms et al, <sup>21</sup> Gosens et al <sup>22</sup>	Epicondylitis/RCT PRP N = 51 vs. N = 49 corticosteroids/12 and 24 mo	Chronic patients (medial region)	3 mL L-PRP (Plt: 4-8 ×; WBC: 6 ×) buffered pH: 7.4 GPS no activation, single blind injection, multiple small depots	VAS, DASH. PRP reduces pain and significantly improves function exceeding the effect of corticosteroid injection
Thanasis et al <sup>23</sup>	Epicondylitis/RCT PRP N = 14 vs. blood N = 14/6 mo	No previous injections, symptoms since 3 mo	3 mL L-PRP (Plt: 5.5 ×; WBC: 6 ×) buffered pH: 7.4 GPS no activation + physiotherapy single US-guided injection, peppering technique	6 wk, 3 mo, and 6 mo VAS, Liverpool Elbow score/ Significant improvement in VAS, only at 6 wk (PRP: 3.8 vs. ABI: 2.5, $P < 0.05$ ); no differences in function
Hechtman et al <sup>27</sup>	Epicondylitis/case series N = 30 patients, 31 cases/6 mo	Unresponsive to conservative treatments for at least 6 mo	3 mL P-PRP CaCl <sub>2</sub> activation single blind injection/1 skin portal and 9 penetrations of the tendon	ASES, Nirschl staging for pain, 1 wk, 1 mo, 3 mo, 6 mo, 12 mo, 24 mo/90% patients met the criteria for success (25% decrease in worst pain). PRP improves function and pain obviating the need for surgery
Mishra and Pavelko <sup>25</sup>	Epicondylitis/cohort PRP N = 15(prospective) vs. controls N = 5 (retrospective)/24 mo	Recalcitrant (medial and lateral region)	3 mL L-PRP (Plt: 4-8 ×; WBC: 6 ×) buffered pH: 7.4 no activation, single blind injection, 5 small depots in the tender area	Significant improvement in PRP group for pain at 8 wk (Mayo elbow score + 60% vs. + 16%, respectively) and at 24 mo + 93% in VAS score and function
Aziza et al <sup>24</sup>	Epicondylitis/RCT N = 30, 15 per group and plantar fasciitis N = 30, 15 per group/steroid vs. PRP/6 wk	Patients with pain and tenderness	L-PRP double spinning (Plt > 2 ×) not reported single blind injection	VAS, DASH, FHSQ/ improvement in both groups. No differences VAS and DASH between groups at 6 wk. No differences VAS and FHSQ between groups at 6 wk
Rha et al <sup>30</sup>	Supraspinatus/RCT, N = 39 25% drop out PRP N = 16, CTRL N = 14/6 mo	Pain > 5/10 since > 6 mo, tendinosis or partial tear < 1 cm (US), unresponsive to conservative treatments for at least 3 mo	3 mL L-PRP, double spinning. Monthly US guided, 2 × PRP injections + dry needling vs. 2 × dry needling	SPADI, US/differences in SPADI Shoulder Pain and Disability Index between both groups at 6 wk (PRP: 34.9 vs. ctrl 21.6), 3 (PRP: 41.2 vs. ctrl 28.2) and 6 mo (PRP: 44.6 vs. ctrl 33.3) from the beginning of the treatment. Differences in

TABLE 1. (continued)

References	Study Design, N/Follow-up	Patient Population	PRP Product and Procedure	Outcome Instruments/Results
Finnoff et al <sup>18</sup>	Prospective and retrospective case series N = 41 upper lower extremity, N = 10 and N = 31/14 mo	Symptoms for over 3 mo unresponsive to conservative treatments for at least 3 mo	2.5-3.5 mL L-PRP: Magellan (22 subjects): 4.8 × Plt; 3.6 × WBC/GPS (19 subjects): 3.6 × Plt; 4.3 × WBC/no activation single US-guided needle tenotomy + depot within pathologic area	the range of shoulder flexion between groups at 3 and 6 mo. Two patients with partial-thickness tear improved to tendinosis without tear (US) 10-point scale for pain and function, US tendon characteristics/echotexture and neovascularisation scales/improvement for function (68%), pain (58%), echotexture (84%), intratendinous calcifications (38%), and neovascularity (82%); 83% of patients were satisfied. Maximum benefits 4 mo postprocedure Changes after 14 mo: upper vs. lower no correlation between location and clinical outcome. No differences between both PRP products. Prechange to postchange in pain -4.1 in function -4.2 (10-point scale)
Akşahin et al <sup>28</sup>	Plantar fasciopathy cohort study prilocaine + PRP N = 30 vs. methylprednisolone + prilocaine N = 30/6 mo	Symptoms since 8-9 mo, unresponsive to conservative treatments for at least 3 mo	3 mL L-PRP(double spin) + 2 mL 2% prilocaine (CaCl <sub>2</sub> -activated injected sequentially. Single blind injection	Roles and Maudsley score (3 wk and 6 mo)/improvement in patient satisfaction and pain at 6 mo, PRP: 3.40, corticosteroids: 2.8. No differences intergroups
Barret and Erredge <sup>29</sup>	Plantar fasciopathy/case series PRP, n = 9/12 mo	Not cortisone within 90 d before PRP	3 mL L-PRP, needling and 1-2 US-guided injection within hypoechoic areas	77.8% of patients were successfully treated. Six patients achieved complete resolution of pain within 2 mo, 1 patient after a second injection

\*Upper extremity: distal triceps: 1, distal biceps: 1, epicondylitis: 8/lower extremity: gluteus medius: 2, proximal hamstring: 2, distal biceps femoris: 1, patellar: 1, popliteus: 1, Achilles midsection: 12, Achilles distal: 2, tibialis posterior: 1, plantar fasciopathy: 9.

†Although published in 2007, these 8 subjects were included in Volpi.<sup>13</sup>

? indicates count not reported; ABI, autologous blood injection; ADL, activities of daily living; AOFAS, American Orthopedic Foot and Ankle Score; ASSES, American shoulder and elbow surgeons; ctrl, control; DASH, disabilities of arm, shoulder and hand; FHSQ, foot health status questionnaire; L-PRP, leukocyte-platelet-rich plasma; Plt, platelets; P-PRP, pure platelet-rich plasma; PRTEE, patient-related tennis elbow evaluation; RCT, randomized control trial; US, ultrasound; VAS, visual analogue scale; SF-36, short form (36) health survey; SPADI, Shoulder Pain and Disability Index; VISA, Victorian Institute of Sports Assessment; WBC, white blood cells.

Even though clinical and structural improvement was reported in noncontrolled studies, the RCT failed to demonstrate superiority of buffered L-PRP + eccentrics over saline + eccentrics.<sup>14,15</sup> These patients were selected before they had tried eccentric exercise therapy, which has been shown to be effective<sup>19</sup>; so, as expected, head-to-head comparisons between the 2 effective treatments failed to show substantive differences. Actually, PRP treatment might be better indicated for recalcitrant tendinopathies which, once exhausted conservative treatments, may necessitate operative intervention.

Yet, it is hoped that approaching trial results from a saline-controlled study for 6 mL of P-PRP (NCT00731068) may shed some light in the above paradoxical results.

### Epicondylitis

Of 8 studies,<sup>18,20-27</sup> 4 were randomized controlled trials. Peerbooms et al<sup>21</sup> presented positive results in a controlled trial of L-PRP versus corticosteroid injection after 12<sup>21</sup> and 24 months.<sup>22</sup> However, Omar et al<sup>24</sup> did not find substantive differences between PRP and corticosteroids, 6 weeks after injection; these results are of limited clinical

value because the study was underpowered (15 subjects per group). Two other randomized studies<sup>20,23</sup> failed to demonstrate that L-PRP was superior to blood injections (control group) at 6 months.

Important to this approach will be upcoming multiarmed phase III trials. For example, 1 recently presented multiarmed clinical trial was designed to detect difference between any of the following arms: PRP injections, steroids, and saline injections (NCT01109446). Another active trial is comparing dextrose prolotherapy, PrT-DMS, PRP injection, with the waitlist (NCT01476605), and further research will uncover differences between PRP, whole blood injection, dry needle fenestration, and the waitlist controls (NCT01668953).

### Plantar Fasciopathy

There were 2 controlled studies with corticosteroids<sup>24,28</sup> and 2 uncontrolled studies.<sup>16,29</sup> One randomized controlled study found significant differences between L-PRP and corticosteroids at 6 weeks<sup>24</sup>; however Akşahin et al<sup>28</sup> conducted a study that failed to show a difference in efficacy at 3 weeks and 6 months between PRP administered after 2% prilocaine and methylprednisolone plus prilocaine injections. Hopefully, 2 active clinical trials controlled with corticosteroids should provide more information about L-PRP (GPS III) (NCT00758641) and P-PRP (ACP, Arthrex) (NCT01614223) efficacy.

### Supraspinatus

Rha et al<sup>30</sup> conducted an RCT, comparing L-PRP plus dry needling with dry needling but they failed to show superiority of L-PRP after 6 months. Currently, there is an active corticosteroid controlled study (NCT01688362) which will be helpful for contrasting the P-PRP formulation (ACP, Arthrex) and the number of injections (2).

Overall, in the available published studies most tendons have been managed with L-PRP (91.7% of the cases, 507). The injected volume varied from 1.5 to 6 mL, but was not related to severity or anatomic location. The commercial protocol GPS II-III (Biomet Manufacturing Corp, Warsaw, IN) for preparing 3 mL of buffered L-PRP was used in 30.5% of patient treated with L-PRP (187 cases). Despite the unexpected homogeneity of PRP formulation across studies, quantitative synthesis through meta-analysis is unfeasible because of inconsistent measures of outcome and lack of randomized treatment comparisons.

### Muscle Injections

Numerous reviews and opinion papers are available on the use of PRP in orthopedics and sports medicine. However, no randomized trials have studied the merits of PRP injections for muscle healing. The search identified only 1 published clinical study<sup>31</sup> and a conference presentation.<sup>32</sup> Wright-Carpenter et al<sup>31</sup> assessed the effects of ACS injections in a nonblinded, nonrandomized case control study. ACS is an autologous liquid serum conditioned by incubation of whole blood with glass beads. It contains signaling proteins that include interleukin-1b (IL-1b), tumor necrosis factor- $\alpha$ , IL-7, fibroblastic growth factor-2, IL-1 receptor antagonist (IL-1Ra), hepatocyte growth factor, platelet-derived growth factor, transforming growth factor, and insulin-like growth factor-1. The experimental group treated with ACS included 17 patients, whereas the control group, which was analyzed retrospectively, included 11 patients who had received Traumeel (Heel Inc.,

Albuquerque, NM)/Actovegin (Nycomed GmbH, Austria) (3:2), that is, homeopathic formulation and amino acids. The Rest Ice Compression Elevation protocol was employed for initial care in both the groups. The tear severity, which was scored as grade 2 with detection of bleeding on MRI, was similar for all control and experimental group. The injected volumes (5 mL) were identical in both groups. The mean number of treatments per patient was 5.4 in the ACS group and 8.3 in the reference group. Return to competition was decided after a strength assessment by standard isokinetic tests. The experimental group returned to competition after 16.6 days, whereas the control group took 22.3 days. In addition, MRI scans taken at 16 days in both groups confirmed that regression of the edema/bleeding was faster in the ACS group.

In a presentation at the 2nd World Congress of Regenerative Medicine, Sanchez et al<sup>32</sup> reported the application of leukocyte-free PRP in 21 muscle injuries of different severities and different anatomic locations. Small tears progressed well with a single application, while more severe tears required 2 to 3 US-guided injections. The injected volume depended on tear severity. These athletes, who played in first division teams of the Spanish Soccer League, resumed normal training activities in half the time needed by matched historical controls.

We all await the results of 2 active clinical trials comparing the injection of autologous PRP with evacuation of the hematoma (NCT) and a recently presented study designed to examine the potential of 1 single PRP injection and rehabilitation program to hasten the recovery of grade 2 hamstring muscle injuries.<sup>33</sup>

## DISCUSSION

Limited data are available to confirm that current PRP therapies work as postulated. Given the lack of large phase II to IV trial, the effectiveness of conservative PRP treatments is not definitely proven. However, the current clinical results may justify the implementation of PRP therapy before considering surgical treatment.

Moreover, there is growing interest in the biological mechanisms underlying PRP injections and, more importantly, how to manipulate these processes for beneficial clinical effect.

In optimizing PRP therapies that recreate the regenerative environment, technical details of the product (formulation, volume, activation) become as important as procedural factors including needling, extensive longitudinal tenotomies, or injection protocols. Regarding the technical characteristics of the product, currently most studies (91.7%) have been performed with nonactivated L-PRP characterized by a mid/high range of platelet concentration (4 to 8  $\times$  peripheral blood). The moderate success of the L-PRP product cannot be universally applied to other PRP products. In fact, whether leukocytes have detrimental effects in orthopedic applications is still controversial. Basic sciences evidence points towards a deleterious effect of neutrophils by synthesizing prostaglandins, reactive oxygen intermediates, elastases, and other proteases that may reduce the activity of GFs and cytokines, and destabilize the fibrin matrix.<sup>34</sup> As basic research has shown fundamental differences between L-PRP and P-PRP, and strongly supports the use of pure PRP in tendons,<sup>35-37</sup> clinical studies to evaluate P-PRP

from a single centrifugation can be considered a low-cost and low-risk treatment option.

As regards the procedure, a further key factor is the number of PRP injections administered. A single injection is deemed more cost-effective. However, in chronic tendinopathies, given the need to control the biological environment and normalizing the otherwise disrupted healing mechanism it may be prudent to use > 1 injection. Hence, sequential injections (every 1 to 4 wk) may be more effective to activate healing, mainly in recalcitrant tendinopathy. Indeed, given the short life-span of GFs and cytokines especially in the presence of metalloproteinases<sup>34</sup> reinjecting PRP is reasonable. Further studies are necessary to determine whether specific locations (loaded or unloaded tendons), type of tendon, for example, broad flat tendon versus narrow circular/ovoid tendon, tendon with synovial sheath versus tendon with paratenon respond better than others.

In more than half of the published tendon studies (12/21), US-guided injections were performed: this allows accurate targeted injection into the sites of sonographic abnormality. However, few studies used US at follow-up. By exploiting the advantages of US during follow-up, clinicians can promptly adjust treatment plans by evaluating changes in hypoechogenicity, structure, or hyperemia on Doppler investigations.

There are no randomized controlled human studies supporting the use of PRP for muscle injuries.<sup>38</sup> Pilot clinical studies indicated that PRP therapies may enhance muscle repair after strain or contusion, and laboratory data indicated that such treatments can enhance diverse aspects of myogenesis.<sup>35</sup> In practice, PRP injections to treat muscle injuries in athletes have produced good results, but the field is underresearched because of the World Anti-Doping Agency prohibition until 2011. The optimal PRP formulation and protocol for treating patients with muscle injuries are unknown. These questions need to be addressed to achieve standardization of the formulations and the procedures for application and to fuel clinical studies.

The acceptance of PRP technology into the market has been determined by the safety profile, ease of use, and familiarity. The true limiting factors are lack of evidence of obvious clinical improvement and reimbursement. As shown in this review, there is no consistency (homogeneity) of study outcomes, and larger double blind randomized trials are needed to take a meta-analytic approach that does not overestimate treatment effects.

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