Systematic Review

Muscle and Tendon Injuries: The Role of Biological Interventions to Promote and Assist Healing and Recovery

Isabel Andia, Ph.D., and Nicola Maffulli, M.D., M.S., Ph.D., F.R.C.S.(Orth)

Purpose: To summarize clinical studies after platelet-rich plasma (PRP) therapy for tendinopathy, plantar fasciopathy, and muscle injuries; to review PRP formulations used across studies; and to identify knowledge deficits that require further investigation. **Methods:** After a systematic review in PubMed, we identified clinical studies assessing PRP efficacy in tendon and muscle during the past decade. We standardized data extraction by grouping studies based on anatomic location; summarized patient populations, PRP formulations, and clinical outcomes; and identified knowledge deficits that require further investigation. **Results:** Overall, 1,541 patients had been treated with PRP in 58 clinical studies; of these, 26 addressed upper limb tendinopathies and 32 addressed the lower limb (810 patients and 731 patients treated with PRP, respectively). The quality of research is higher for the upper limb than for the lower limb (23 controlled studies, of which 17 are Level I, *v* 19 controlled studies, of which 6 are Level I, respectively). Patients have been treated mostly with leukocyte-platelet–rich plasma, except in the arthroscopic management of the rotator cuff. The safety and efficacy of PRP for muscle injuries has been addressed in 7 studies including 182 patients. Differences across results are mainly attributed to dissimilarities between tissues and different stages of degeneration, numbers of PRP applications, and protocols. **Conclusions:** Given the heterogeneity in tendons and tendinopathies, currently, we are not able to decide whether PRP therapies are useful. Despite advances in PRP science, data are insufficient and there is a clear need to optimize protocols and obtain more high-quality clinical data in both tendinopathies and muscle injuries before making treatment recommendations. **Level of Evidence:** Level IV, systematic review of Level I through IV studies.

See commentary on page 1016

The current demographic changes in developed countries, including Europe and United States, are producing an alarming burden of degenerative musculoskeletal conditions. Though not as pervasive as osteoarticular conditions, tendinopathies are insidious. Because of its expanding prevalence, tendon pathology is becoming a major focus for research aiming to elucidate its cause and pathogenesis and to identify minimally invasive biological interventions.[1]

It is incumbent on anyone interested in implementing biological interventions such as platelet-rich plasma (PRP) or cell therapies to understand the characteristics and the rationale for their application to identify hurdles to achieve successful tissue repair.[2] How to intervene biologically is chiefly driven by our understanding of the pathologic processes underlying the condition; thus basic hypotheses are shared in both PRP and cell therapies. In tendinopathy the failed-healing hypothesis suggests that repetitive stresses lead to small injuries within the tendon that fail to heal before further trauma occurs. Difficulties in achieving healing arise in tissues characterized by a low cell number and low extracellular matrix turnover.[3]

Thus, broadly speaking, tendon regeneration can be achieved by increasing cell numbers and/or enhancing tendon cell anabolism (collagen synthesis). As a dominant cell type in tendons, tenocytes are responsive to molecular environmental stimuli that modulate

From the Regenerative Medicine Laboratory, BioCruces Health Research Institute, Cruces University Hospital (I.A.), Barakaldo, Spain; Department of Musculoskeletal Disorders, University of Salerno School of Medicine and Dentistry (N.M.), Salerno, Italy; Queen Mary University of London (N.M.), London, England; Barts and The London School of Medicine and Dentistry (N.M.), London, England; and Centre for Sports and Exercise Medicine, Mile End Hospital (N.M.), London, England.

The authors report that they have no conflicts of interest in the authorship and publication of this article.

Received July 15, 2014; accepted November 13, 2014.

Address correspondence to Nicola Maffulli, M.D., M.S., Ph.D., F.R.C.S.(Orth), Queen Mary University of London, 275 Bancroft Road, London E1 4DG, England. E-mail: n.maffulli@qmul.ac.uk

0749-8063/14609/$36.00

http://dx.doi.org/10.1016/j.arthro.2014.11.024

proliferation and collagen synthesis. Biological therapies, such as cell therapies, are designed to augment cell numbers in the injured tissue by exogenous expansion and grafting. Two biotechnology companies are at the forefront of cell product development for tendons. An autologous tenocyte therapy—Ortho-ATI—is currently available from Orthocell, Murdoch, Australia, and a phase I/II double-blind randomized trial is planned in the Netherlands (NCT01343836). In addition, autologous dermal fibroblasts are manufactured by Innovacell Biotechnologie AG, Innsbruck, Austria, and have been explored for tendon augmentation based on their collagen-producing capabilities. A systematic literature review of human studies of cell therapy in tendons[4] disclosed 4 clinical studies. Three of these, sponsored by Innovacell, examined skin fibroblast injections in 3 anatomic locations—elbow,[5] patellar,[6] and Achilles tendons[7]—showing safety and potential benefits in the short-term. In addition, human bone marrow mesenchymal stem cells have been safely injected in rotator cuff tears with promising results in a limited number of patients.[8] The field remains otherwise under-researched.

Alternatively, PRP therapies, designed to modify the biological milieu and target tenocyte activation, have been explored in both experimental and clinical studies. Previous research has shown that tenocytes from tendinopathic tissue, when exposed to PRP releasates, proliferate and synthesize extracellular matrix molecules (including type I, II, and X collagen; decorin; aggrecan; and biglycan), essential to tendon function.[9,10] Moreover, PRP provides protection against oxidative stress and modulates the angiogenic and inflammatory conditions of tendons, as well as the anabolic capabilities of tenocytes.[11,12] Several signaling proteins released from PRPs induce neotendon formation, including fibroblast growth factor 2, transforming growth factor β, insulin-like growth factor 1, vascular endothelial growth factor, platelet-derived growth factor, and bone morphogenetic protein 2.[2] PRP enhances tendon cell growth and migratory capacity and combats the oxidative stress leading to cell apoptosis.[13,14]

PRP can enhance the self-healing potential of tissues by proper activation of endogenous local stem cells. Though relatively low in number, tendon stem cells (TSCs) also play a critical role in tendon regeneration because of their ability to self-renew and differentiate into tenocytes, thereby replacing tenocytes lost from apoptosis.[15] Importantly, the number of TSCs may be reduced in tendinopathy, and the TSCs may differentiate into non-tendon cells.[16] Migration and tenogenic differentiation of PRP-treated tendon precursor cells are currently emphasized by experimental studies.[17,18]

Other than increasing cell numbers and differentiation, PRP enhances tendon regeneration by improving cell anabolism.[2] Recent estimates of the rate of replacement for collagen in the Achilles tendon concluded that tendon tissue is practically inert.[19] Quite the opposite, the muscle tissue (musculus psoas major), used as a comparator in this study, exhibits high turnover rates (i.e., is constantly being replaced).

The biological mechanisms underlying muscle regeneration are similar, but in this context PRP aims primarily to potentiate migration and differentiation of satellite cells while modulating inflammation, in doing so tailoring the microenvironment for efficient repair.[20,21] Although experimental research supports PRP intervention in tendons and muscles, there is a clear need (1) to summarize clinical results after PRP therapy for tendinopathy and muscle injuries, (2) to review PRP formulations used across studies, (3) to provide treatment recommendations based on the protocols described in the best available literature, and (4) to identify knowledge deficits that require further investigation.

Methods

Search for Clinical Data

We searched Medline via PubMed with combinations of the search terms "platelet rich plasma," "tendon," "rotator cuff," "epicondylitis," "fasciitis," "Achilles," "patellar," "skeletal muscle," "muscle injuries," "sports," and "human" from January 2003 to August 2014. We also searched our own files. Only articles published in English were reviewed.

Study Selection and Data Extraction

We included all original articles describing the use of PRP in tendon and muscle injuries. All types of management (i.e., conservative, arthroscopic surgery, or open surgery) and controlled and uncontrolled studies were included. Conference proceedings and case reports were excluded.

We extracted and tabulated the following data: study design, type of participants, type of intervention (i.e., PRP formulation and number of injections), follow-up, and type of outcome measures. Results were synthesized by grouping the studies based on anatomic locations as upper limb lesions, including epicondylitis and rotator cuff conditions, and lower limb, including the patellar tendon, Achilles tendon, and plantar fascia.

Results

Upper Limb Tendon Injuries

Overall, in the reviewed clinical studies, 1,541 patients were treated for tendinopathy (including plantar fasciitis). Most research focused on upper limb pathology, with 9 controlled studies[22-30] and 2 case series on epicondylitis,[31,32] 13 controlled studies on arthroscopic management of the rotator cuff,[33-45] 2 controlled studies evaluating conservative management,[46,47] and 1 case series[48] (Table 1).

Table 1. Platelet-Rich Plasma Therapies in Clinical Studies of Upper Limb Tendinopathy (Epicondylitis and Rotator Cuff Disease)

Study (Year)	LOE	Study Design and Patient Population	Intervention and PRP Formulation	Outcome Measurements	Follow-up	Results
Epicondylitis (conservative management)						
Raeissadat et al.[22] (2014)	I	RCT: patients with chronic lateral epicondylitis receiving PRP (n = 31) or autologous blood (n = 30)	2 mL of L-PRP (PLT: 4×-6×) and 2 mL of 1% lidocaine *v* 2 mL of autologous blood and 2 mL of 1% lidocaine	VAS, modified Mayo performance index, and PTT	4 wk, 8 wk, 6 mo, and 12 mo	Both treatments are effective. PRP is not superior to autologous blood.
Krogh et al.[23] (2013)	I	RCT with 3 arms: patients with symptoms for >3 mo; PRP (n = 20), saline solution (n = 20), and glucocorticoid (n = 20)	3-4 mL of L-PRP (PLT: 4×-8×, WBC: 6×), buffered; pH 7.4; no activation Saline solution: 3 mL of glucocorticoid (1 mL of triamcinolone + 2 mL of lidocaine)	PRTEE score (pain and function analyzed separately), VAS (pain and pain duration caused by treatment), US, and color Doppler activity	3 mo	No differences
Mishra et al.[24] (2014)	I	Multicenter RCT: PRP (n = 116) *v* bupivacaine (n = 114) Patients with symptoms for >3 mo; failed conventional therapy	3 mL of L-PRP (PLT: 4×-8×, WBC: 6×), buffered; pH 7.4; no activation (0.5% bupivacaine and epinephrine to block injection site) Bupivacaine, 2-3 mL	VAS and PRTEE score	4, 8, 12, and 24 wk	Significant VAS improvement at 24 wk in PRP group; fewer patients reporting tenderness in PRP group at 12 and 24 wk; percent success rate at 24 wk (reduction <25% in VAS) significantly higher in PRP group
Omar Aziza et al.[25] (2012)	I	RCT: n = 15 per group Patients with pain and tenderness	L-PRP (PLT: >2×) *v* corticosteroid Volume, activation: NR	VAS and DASH score	6 wk	No significant differences between the 2 groups
Creaney et al.[26] (2011)	I	RCT: PRP (n = 80) *v* blood (n = 70) Resistant patients, PRTEE score of 49	1.5 mL of L-PRP (PLT: 2.8×), single spinning, buffy coat Monthly US-guided injections (2) into clefts of hypoechoic areas (no dry needling)	PRTEE score	6 mo	Improvement in both groups at 6 mo but no difference between groups; higher proportion of failures (removed for surgery) in ABI group (12 of 17) *v* PRP group (7 of 24); success rate (50% improvement) at 6 mo of 66% in PRP group *v* 72% in ABI group
Peerbooms et al.[27] (2010) and Gosens et al.[28] (2011)	I	RCT: PRP (n = 51) *v* corticosteroids (n = 49) Chronic patients (medial region)	3 mL of L-PRP (PLT: 4×-8×, WBC: 6×), buffered; pH 7.4 Single-blind injection; multiple small depots	VAS DASH score	12 and 24 mo 12-24 mo	PRP reduces pain and improves function exceeding the effect of corticosteroid injection.
Thanasas et al.[29] (2011)	I	RCT: PRP (n = 14) *v* blood (n = 14) No previous injections; symptoms for 3 mo	3 mL of L-PRP (PLT: 5.5×, WBC: 6×), buffered; pH 7.4; GPS with no activation + physiotherapy Single US-guided injection; peppering technique	VAS and Liverpool elbow score	6 wk, 3 mo, and 6 mo	Significant improvement in VAS only at 6 wk (3.8 in PRP group *v* 2.5 in ABI group, $P < .05$); no differences in function

(continued)

Table 1. Continued

Study (Year)	LOE	Study Design and Patient Population	Intervention and PRP Formulation	Outcome Measurements	Follow-up	Results
Mishra and Pavelko[30] (2006)	III	PRP cohort (n = 15) (prospective) *v* control (n = 5) (retrospective) Recalcitrant (medial and lateral region)	3 mL of L-PRP (PLT: 4×-8×, WBC: 6×), buffered; pH 7.4; no activation Single-blind injection, 5 small depots in tender area	—	24 mo	Significant improvement in PRP group for pain at 8 wk (Mayo elbow score: +60% *v* +16%) and at 24 mo (+93% in VAS score and function)
Chaudhury et al.[31] (2013)	IV	Case series: N = 6 US diagnosis of extensor tendinosis; partial tear of extensor (<50%)	3 mL of L-PRP (PLT: 4×, WBC: 4×; Harvest SmartPrep, Terumo Cosporation, Tokyo, Japan) Single US-guided injection	Contrast US: QLAB software (quantitative; Philips, Amsterdam, The Nederlands), MVI, and microvascular imaging	1 and 6 mo	Improved extensor tendon morphology
Hechtman et al.[32] (2011)	IV	Case series: N = 30 patients (N = 31 cases) Unresponsive to conservative treatment for ≥6 mo	3 mL of P-PRP $CaCl_2$ activation Single-blind injection/1 skin portal and 9 penetrations of tendon	ASES and Nirschl staging for pain	1 wk, 1 mo, 3 mo, 6 mo, 12 mo, and 24 mo	Ninety percent of patients met the criteria for success (25% decrease in worst pain). PRP improves function and pain, obviating the need for surgery.
Shoulder: arthroscopy						
Malavolta et al.[33] (2014)	I	RCT: n = 27 per group Complete tears (retraction <3 cm)	10 mL of liquid PRP (1.5 mL of autologous thrombin and 0.8 mL of 10% $CaCl_2$)	Constant and UCLA scores VAS	3, 6, 12, and 24 mo 24 mo	No differences at any time point
Antuña et al.[34] (2013)	I	Pilot RCT: n = 14 per group Massive full-thickness tears	P-PRP gel	VAS, Constant score, and MRI	1 yr	No differences
Ruiz-Moneo et al.[35] (2013)	I	RCT: PRP (n = 32) *v* control (n = 31) Full-thickness tears	P-PRP gel	UCLA score and MRI	1 yr	No differences between groups
Jo et al.[36] (2013)	II	Prospective cohort: n = 24 per group Massive full-thickness tears	3× P-PRP gel	MRI, CSA, CTA, ROM, and pain	1 yr	Differences in overall function and CSA; better structural outcome and smaller CSA in PRP group; no other differences
Weber et al.[37] (2013)	I	RCT: n = 30 per group All patients underwent an associated acromioplasty. Seven patients in the PRFM group underwent associated biceps tenodesis, and 1 underwent associated acromioclavicular repair. Five patients in the control group underwent biceps tenodesis, and 1 had a superior labral anteroposterior lesion.	PRFM (P-PRP fibrin)	ROM, UCLA score, SST score, and VAS	3, 6, 9, and 12 mo	No differences in perioperative morbidity, structural integrity, or clinical outcome
Gumina et al.[38] (2012)	I	RCT: n = 40 per group Large rotator cuff tears	P-PRP gel	Constant, MRI, and SST score	13 mo	No differences in function but better repair integrity in PRP group
Rodeo et al.[39] (2012)	II	RCT: PRP (n = 40) *v* control (n = 39)	P-PRP fibrin (PRFM) (moderate to low platelet concentration)	ASES score and Doppler US	—	Better in control group

(continued)

Table 1. Continued

Study (Year)	LOE	Study Design and Patient Population	Intervention and PRP Formulation	Outcome Measurements	Follow-up	Results
Bergeson et al.[40] (2012)	III	Prospective cohort with historical control: N = 38/2 per group High-risk tears	P-PRP fibrin (PRFM) (moderate to low platelet concentration)	Constant, WORC, SANE, ASES, and UCLA scores	1 yr	No differences; higher retear rate in PRFM group; 2 of 16 patients in PRFM group had infections
Jo et al.[41] (2011)	II	Prospective cohort: N = 42/2 per group Full-thickness tears (all sizes)	P-PRP gel	ASES, Constant, UCLA, DASH, SST, and SPADI scores	3, 6, 12, and 16 mo	No differences in outcomes
Randelli et al.[42] (2011)	I	RCT: PRP (n = 26) *v* control (n = 27) Full-thickness tears	GPS, L-PRP, and high leukocyte and platelet concentrations	SST score, UCLA score, Constant score, and SER	3, 6, 12, and 24 mo	No differences in any score at any time; grade 1 and 2 SER better in PRP group at 6, 12, and 24 mo
Castricini et al.[43] (2011)	I	RCT: PRP (n = 43) *v* control (n = 45) Isolated tears	P-PRP fibrin (moderate to low platelet concentration)	Constant score and MRI	16 mo	No differences between groups
Charousset et al.[44] (2014)	III	Case control: n = 27 per group	6 mL of L-PRP and autologous thrombin	Constant score, UCLA score, SST score, and MRI	24 mo	No differences; no differences in retear rate; smaller iterative tears in L-PRP group
Barber et al.[45] (2011)	III	Case control: n = 20 per group Full-thickness tears	2× P-PRP fibrin (moderate to low platelet concentration)	MRI, ASES score, SANE score, and Constant score	31 mo	Lower retear rates on MRI; no differences in other outcomes
Shoulder: conservative management						
Rha et al.[46] (2013)	I	RCT: N = 39 with 25% dropout; PRP (n = 16) *v* control (n = 14) Pain >5 of 10 for >6 mo, tendinosis or partial tear <1 cm (US), unresponsive to conservative treatments for ≥3 mo	3 mL of L-PRP, double spinning Monthly US-guided 2× PRP injections + dry needling *v* 2× dry needling	SPADI score and US	6 mo	Differences in SPADI score between both groups at 6 wk (34.9 in PRP group *v* 21.6 in control group), 3 mo (41.2 in PRP group *v* 28.2 in control group), and 6 mo (44.6 in PRP group *v* 33.3 in control group) from beginning of treatment; differences in range of shoulder flexion between groups at 3 and 6 mo; 2 patients with partial-thickness tears improved to tendinosis without tears (US)
Kesikburun et al.[47] (2013)	I	RCT: n = 20 per group Chronic tendinosis or partial tear	5 mL of L-PRP (GPS system), PRP *v* saline solution	WORC score, SPADI score, and VAS	3, 6, 12, and 24 wk and 1 yr	No differences between groups
Scarpone et al.[48] (2013)	IV	Case series: N = 18 Tendinopathy refractory to physical therapy and corticosteroids	Single injection, 3 mL of 1% lidocaine and 3.5 mL of PRP	—	—	VAS improvement at weeks 12 and 52; functional shoulder test significantly improved; largest effect on external rotation at week 12; MRI appearance improved by 1 to 3 points; 17 patients were completely satisfied (n = 12) or satisfied (n = 5) and 1 was unsatisfied

ABI, autologous blood injection; ASES, American Shoulder and Elbow Surgeons; CTA, computed tomographic arthrography; DASH, Disabilities of the Arm, Shoulder and Hand; L-PRP, leukocyte-platelet–rich plasma; LOE, level of evidence; MRI, magnetic resonance imaging; MVI, microvascular imaging; NR, not reported; PLT, platelet concentration; PRFM, platelet-rich fibrin matrix; P-PRP, pure platelet-rich plasma; PRTEE, Patient-Rated Tennis Elbow Evaluation; RCT, randomized controlled trial; ROM, range of motion; SANE, Single Assessment Numeric Evaluation; SER, strength in external rotation; SPADI, Shoulder Pain and Disability Index; SST, Simple Shoulder Test; UCLA, University of California, Los Angeles; US, ultrasonography; VAS, visual analog scale; WBC, white blood cell concentration; WORC, Western Ontario Rotator Cuff Index.

Epicondylitis

A successful treatment for epicondylitis is deemed to improve pain and function in daily activities. PRP has been compared with corticosteroids, local anesthetics, and autologous blood. When comparing leukocyte-platelet—rich plasma (L-PRP) with corticosteroids in a controlled randomized trial, Peerbooms and colleagues presented positive results at 6 and 12 months[27] and 24 months after treatment.[28] In contrast, 2 other studies did not find significant differences at 6 weeks[25] or 3 months after treatment.[23] However, these results are of limited clinical value because these studies were presumably underpowered.

When comparing PRP with an anesthetic (bupivacaine), in a multicenter study, Mishra et al.[24] found a higher percentage of responders in the PRP group, 24 weeks after treatment. Two other randomized studies failed to show that L-PRP was superior to blood injections (control group) at 6 months.[26,29] A recent meta-analysis conducted by our group highlights difficulties in reaching conclusions and recommendations regarding epicondylitis, given the heterogeneity of the comparators.[49]

Upcoming research includes 3-armed studies comparing PRP injections, steroids, and saline solution injections (NCT01109446); comparing dextrose prolotherapy, PrT-DMS (prolotherapy, 50% dextrose + 5% morrhuate sodium), and PRP injection with traditional conservative management (NCT01476605); and comparing PRP, whole blood injection, and dry needle fenestration with traditional conservative management (NCT01668953). In addition, the number of injections may be crucial; thus our group is exploring the efficacy of 2 biweekly injections of pure PRP associated with needle tenotomy compared with lidocaine and needle tenotomy.[50]

Rotator Cuff

Rotator cuff degeneration is prevalent, and repair is challenging because of the complex biomechanical environment of the shoulder; moreover, the need to modify diverse intrinsic and extrinsic factors most often may require combinatory approaches such as arthroscopic surgery and PRP.

Arthroscopic Management. The outcomes of 363 patients were examined after arthroscopic management in 11 controlled studies.[33-45] Chahal et al.[51] performed a systematic review with quantitative synthesis including 5 of these studies, 2 randomized[42,43] and 3 nonrandomized,[40,41,45] and could not confirm any effect on overall retear rates. However, they found a trend toward lower retear rates when analyzing small- and medium-sized tears. Later on, 6 controlled studies had been published but the simple addition of PRP clots appeared to be insufficient to augment repair. Jo et al.[41] showed a decreased retear rate and increased cross-sectional area compared with arthroscopic repair without PRP in patients with massive tears. Importantly, the amount of PRP used in their study was 3-fold the amount used in the other studies (i.e., 3× platelet-rich fibrin matrix [PRFM] instead of 1× PRFM).

Conservative Management. Flat acromions may not need surgical decompression and thus are better treated conservatively. Rha et al.[46] conducted a randomized controlled trial comparing L-PRP plus dry needling with dry needling alone but failed to show superiority of L-PRP after 6 months. Kesikburun et al.[47] compared a single infiltration of 5 mL of L-PRP into the subacromial space plus exercise versus exercise alone in 20 patients but could not find differences in terms of quality of life, pain, disability, and range of motion. Currently, there is an active corticosteroid-controlled study (NCT01688362) that will be helpful for contrasting posterior glenohumeral injections of pure PRP (ACP; Arthrex, Naples, FL) and the number of injections (2 in this forthcoming study).

Lower Limb Tendon Injuries

Patellar Tendinopathy

A total of 208 patients, mostly athletes, were treated with PRP injections in 2 randomized controlled studies,[52,53] 1 cohort study,[54] and 5 case series.[55-59] All studies but one[56] used changes in Victorian Institute of Sports Assessment—Patella (VISA-P) outcome measures at 6 to 12 months after treatment (1 case series had a follow-up of up to 4 years). The VISA-P is a patient self-reported score with an emphasis on pain, function, and return to sports activities (Table 2).

PRP combined with needling was superior to dry needling at 12 weeks but not at 26 weeks. However, the PRP group at 26 weeks included merely 9 patients.[52] Another randomized trial included a total of 46 patients who were treated with 2 injections of pure PRP every other week; 3 extracorporeal shockwave therapy sessions were used as a comparator.[53] This study showed VISA-P improvement at 6 and 12 months but not at 2 months after treatment. The rate of responder patients was higher for PRP than extracorporeal shockwave therapy.

Three injections of L-PRP did not show a pain decrease but showed enhanced function when compared with physiotherapy.[54] More recently, in a case series of 43 patients, the same authors, using an identical treatment but with ultrasonography (US) guidance, reported better results over time (3 to 4 years).[56] Corroborating the study of Gosens et al.,[58] which compared PRP effects in refractory versus non-refractory patients, worse outcomes were found in patients with a longer history of the disease. Otherwise,

Table 2. Platelet-Rich Plasma Therapies in Clinical Studies of Lower Limb Conditions (Patellar Tendinopathy, Achilles Tendon Conditions, and Plantar Fasciitis)

	LOE	Study Design and Patient Population	Intervention and PRP Formulation	Outcome Measurements	Follow-up	Results
Patellar tendon (conservative management)						
Dragoo et al.[52] (2014)	I	RCT: PRP (n = 9) v dry needling (n = 12) Persistence of symptoms after 6 wk (12 sessions) of physical therapy with eccentric exercises	6 mL of L-PRP (PLT: 4×-8×, WBC: 6×), buffered; pH 7.4; no activation Single injection + dry needling *v* dry needling All patients received 3 mL of bupivacaine with epinephrine	VISA-P, Tegner, Lysholm, and SF-12 scores	12 and 26 wk	PRP group superior to dry needling at 12 wk but not at 26 wk
Vetrano et al.[53] (2013)	I	RCT: n = 23 per group Athletes, chronic (>6 mo) and recalcitrant	2 mL of P-PRP (2 injections 1 wk apart) *v* ESWT (3 sessions)	VAS, VISA-P score, and Blazina scale	2, 6, and 12 mo	VISA-P and VAS better in PRP group at 6 and 12 mo; no differences at 2 mo; Blazina scale better in PRP group at 12 mo; higher success rates in PRP group (% responders) at 12 mo
Filardo et al.[54] (2010)	III	Nonrandomized study: PRP (n = 15) *v* physiotherapy (n = 16) (matched for age, sex and sport level) Chronicity >3 mo and recalcitrant to conservative and surgical treatment only in PRP group	Blood bank: 5 mL of L-PRP (PLT: 6×, WBC: NR) Activated Ca^{2+} mEq/dose 3 blind injections biweekly + physical therapy	EQ-VAS and Tegner score	6 mo	No significant improvement in PRP group for EQ-VAS and pain level; significant improvement in Tegner score in PRP group (+39 *v* 20%)
Charousset et al.[55] (2014)	IV	Case series: N = 28, 17 professional athletes and 11 semiprofessional	3 injections 1 wk apart, P-PRP (PLT: 2×)	VISA-P score, VAS, Lysholm score, and MRI	1 and 3 mo	Recovery of normal tendon structure; significant improvement in all scores at 2 yr
Filardo et al.[56] (2013)	IV	Case series: N = 43 Athletes, chronic	3 US-guided injections of 5 mL of L-PRP, biweekly	VISA-P score, Blazina scale, EQ-VAS, Tegner score, and US	4 yr	VISA-P increased over time. Eighty percent were satisfied and resumed previous SA.
van Ark et al.[57] (2013)	IV	Case series: N = 5 patients, 6 tendons Athletes, symptoms for >12 mo, VISA-P <80, US hypoechogenicity, recalcitrant to ≥12 wk of eccentric training	P-PRP (PLT: 1.7×) (ACP, Arthrex) Single US-guided injection + physical therapy	VISA-P score, VAS during DA, and functional test	6 mo	5 of 6 tendons showed improvement of ≥30 points on VISA-P after 6 mo
Gosens et al.[58] (2012)	IV	Case series: N = 36; subgroups were refractory (n = 14) *v* non-refractory (n = 22) Resistant to conservative and surgical treatment (n = 14), resistant but no injections, no responders to eccentric exercise in any group	3 mL of L-PRP (PLT: 4×-8×, WBC: 6×), buffered; pH 7.4; + bupivacaine/no activation Single-blind injection/1 skin portal and 5 penetrations of tendon	VISA-P score, ADL, and VAS	18 mo	Clinical improvement in refractory and non-refractory patients; better results in latter group
Volpi et al.[59] (2007)	IV	Case series: N = 8 Young athletes, third proximal recalcitrant tendinopathy for ≥1 yr	3 mL of L-PRP (PLT: 4×-8×, WBC: 6×), buffered; pH 7.4 GPS III/no activation + rehabilitation Single-blind injection	VISA-P score and MRI	4 mo	VISA improvement (91%); reduction in irregularity in 80% of treated tendons (MRI, 4 mo)

(continued)

Table 2. Continued

	LOE	Study Design and Patient Population	Intervention and PRP Formulation	Outcome Measurements	Follow-up	Results
Achilles tendon: conservative management						
Kearney et al.[60] (2013)	I	Pilot randomized trial: n = 10 per group Chronic	L-PRP single injection *v* eccentric loading	VISA-A score	6 wk, 3 mo, and 6 mo	76.0 (95% CI, 58.3 to 93.7) and 57.4 (95% CI, 38.1 to 76.7) for exercise group at 6 mo
de Vos et al.[61] (2010) and De Jonge et al.[62] (2011)	I	RCT: PRP (n = 27) *v* saline solution (n = 27) Minimal duration of symptoms of 2 mo, excluded if previous full eccentric program or PRP	4 mL of L-PRP (PLT: 4×-8×, WBC: 6×), buffered; pH 7.4; no activation and eccentric exercises Single US-guided injection	VISA-A score and Doppler US	6 mo (de Vos et al.) and 12 mo (de Jonge et al.)	No differences in VISA and US improvement were found; 59% of patients were satisfied in both groups.
Murawski et al.[63] (2014)	IV	Case series: N = 32 Midportion recalcitrant to conservative treatment	Single PRP injection	FAOS and SF-12 score	6 mo	Of patients, 78% resumed SA and DA and avoided intervention.
Filardo et al.[64] (2014)	IV	Case series: N = 27 Midportion, chronic recalcitrant	3 injections of 5 mL of L-PRP (PLT: 5×, leukocytes: 1.2×) with 2-wk interval	Blazina scale, VISA-A score, EQ-VAS, and Tegner score	2 mo, 6 mo, and 4.5 yr	Significant improvement at 2 and 6 mo; stable results at 4.5 yr
Kaniki et al.[65] (2014)	III	Retrospective comparative study: PRP (n = 73) *v* control (n = 72)	2 injections of PRP during first 2 wk after injury Control: nonoperative treatment, accelerated rehabilitation	Isokinetic plantar flexion, ROM, AOFAS score or calf circumference, and Leppilahti score	1 and 2 yr	No differences at 1 or 2 yr
Deans et al.[66] (2012)	IV	Case series: 26 patients, 2 bilateral Chronic	1 injection in 24 patients, 2 injections in 2 patients, P-PRP + rehabilitation	VAS, FAOS, and QOL	Minimum, 6 mo	Improvement in all parameters
Gaweda et al.[67] (2010)	IV	Case series: N = 14 patients, 15 tendons All patients seeking treatment, systemic inflammation excluded	3 mL of L-PRP (PLT: 5.5×, WBC: 6×) (Curasan, Kleinostheim, Germany) Single US-guided injection into hypoechogenic areas	AOFAS and VISA scores	6 wk, 3 mo, 6 mo, and 18 mo	Significant improvement in AOFAS (+41) and VISA (+72) scores; reduction of tendon thickness and hypoechoic areas (US); improvement in qualitative grayscale US characteristics
Monto[68] (2012)	IV	Case series: N = 36 patients	PRP Single US-guided injection	—	24 mo	The mean 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 after treatment.
Achilles tendon: surgical management						
Sánchez et al.[69] (2007)	III	Prospective cohort with retrospective controls: PRP (n = 6) *v* control (n = 6) Athletes (recreational and professional)	P-PRP	CSA and VISA-A score	12 mo	Reduced CSA in operated *v* contralateral in PRP group; faster return to SA
Schepull et al.[70] (2011)	II	RCT: PRP (n = 16) *v* control (n = 14)	L-PRP	Elasticity modulus and heel raise	12 mo	Inferior in PRP group

(continued)

Table 2. Continued

	LOE	Study Design and Patient Population	Intervention and PRP Formulation	Outcome Measurements	Follow-up	Results
Achilles and patellar tendons (conservative management)						
Ferrero et al.[71] (2012)	IV	Case series: Achilles (n = 30) + patellar (n = 28) tendons Competitive and recreational athletes, resistant to conservative treatments	Blood bank: 6 mL of L-PRP (PLT: 5×, WBC: 6×)/thrombin activation US guided/2 scarifications and 2 injections (3-wk interval)	VISA-P score, VISA-A score, and US	6 mo	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.[72] (2010)	IV	Case series: patella (n = 13 tendons) and Achilles (n = 4 tendons) 1 epicondylitis, 1 quadriceps Case series: N = 15 athletes, 19 tendons All with recalcitrant tendinopathy for ≥1 yr Nine young athletes the others recreational	3 mL of L-PRP (PLT: 4×-8×, WBC: 6×), buffered; pH 7.4; no activation; GPS and rehabilitation Single US-guided injection	VISA-P score and MRI	24 mo	Improvement in VISA score (+37) and reductions in abnormalities in 80% of treated tendons (MRI); improvement of clinical symptoms was maintained for ≥2 yr after treatment; improvement less marked in Achilles tendons
Upper and lower limb (conservative management)						
Finnoff et al.[73] (2011)	IV	Prospective and retrospective case series: N = 41 patients, 10 upper and 21 lower limbs Chronic recalcitrant	L-PRP + tenotomy	Changes in pain, function, and tendon characteristics	14 mo	Mean function improvement, 68%; improvement in worst pain scores, 58%; 84% had improvement in echotexture; 82% had decreased intratendinous vascularity
Plantar fasciitis (conservative management)						
Monto[74] (2014)	I	Randomized: n = 20 per group Resistant (4 mo) to conservative management	3 mL of PRP; control group, Depo-Medrol cortisone (Pfizer, New York, NY)	AOFAS score	3, 6, 12, and 24 mo	PRP more effective than cortisone
Shetty et al.[75] (2014)	III	Prospective comparative study: 30 patients per group Recalcitrant	8 mL of L-PRP, 1 injection; control, 3 mL, 40 mg triamcinolone, and 2% lidocaine	VAS, AFAS, and FADI	3 mo	Better improvement in PRP group
Akşahin et al.[76] (2012)	II	Cohort study: n = 30 per group Symptoms for 8-9 mo, unresponsive to conservative treatments for ≥3 mo	3 mL of L-PRP (double spin) + 2 mL of 2% prilocaine ($CaCl_2$ activated, injected sequentially); control group, methylprednisolone Single-blind injection Prilocaine in both groups	Roles and Maudsley score	3 wk and 6 mo	Improvement in patient satisfaction and pain at 6 mo: 3.40 in PRP group and 2.8 in corticosteroid group; no differences between groups
Omar Aziza et al.[25] (2012)	I	Randomized: n = 15 per group Patients with pain and tenderness	L-PRP (PLT: >2×) Volume: NR Activation: NR *v* corticosteroid	VAS and FHSQ score	6 wk	No differences between groups

(continued)

Table 2. Continued

	LOE	Study Design and Patient Population	Intervention and PRP Formulation	Outcome Measurements	Follow-up	Results
Kim and Lee[77] (2013)	II	Randomized single blind: PRP (n = 10) *v* control (n = 11) Chronicity >6 mo, unresponsive to conservative treatment	PRP (PLT: 7.6×), 2 injections, 2-wk interval Control: dextrose prolotherapy, 2 injections	FFI score	2-6 mo	No significant difference: 30.4% in PRP group *v* 15.1% in control group
Wilson et al.[78] (2014)	IV	Case series: N = 24 Chronic recalcitrant	PRP injection	32-wk FAAM, Foot-SANE score, and SF-12 score		Improvement in all outcome measures
Martinelli et al.[79] (2013)	IV	Case series: N = 14 Chronic recalcitrant fasciitis, evidence of calcaneal spur (5 athletes)	Three injections of P-PRP weekly, <5 mL	Roles and Maudsley score and VAS	12 mo	Significant decrease in VAS; excellent in 9, good in 2, acceptable in 2, and poor in 1
Kumar et al.[80] (2013)	IV	Case series: N = 44 patients (50 heels) Recalcitrant	PRP injection	Roles and Maudsley score, VAS, and AOFAS score	3 and 6 mo	Significant improvement in MRI, VAS, and AOFAS score at 6 mo
O'Malley et al.[81] (2013)	IV	Case series: N = 23 Chronic 6 mo	2-3 mL of L-PRP (1-2 injections; if 2 injections, 4-wk interval)	FAOS, SF-12 score, VAS, QOL, DA, and SA	4 wk	Significant improvement in QOL, VAS, and SF-12 score; of 23 patients, 5 went on to endoscopic release
Ragab and Othman[82] (2012)	IV	Case series: N = 25	5 mL of PRP (6×-8×)	Functional limitations	2 wk, 3 mo, 6 mo, and 1 yr	US showed decreased thickness of medial and central bands; no functional limitations in 60%; minimal limitations in 32%
Barret and Erredge[83] (2004)	IV	Case series: N = 9 No cortisone within 90 d before PRP	3 mL of L-PRP, needling and 1-2 US-guided injections within hypoechoic areas	—	12 mo	Of patients, 77.8% were successfully treated. Six patients achieved complete resolution of pain within 2 mo; 1 patient, after a second injection.

ADL, activities of daily living; AFAS, Foot & Ankle Score; AOFAS, American Orthopaedic Foot and Ankle Score; $CaCl_2$, calcium chloride; CI, confidence interval; DA, daily activities; EQ-VAS, EuroQol visual analog score; ESWT, extracorporeal shockwave therapy; FAAM, foot and ankle ability measure scoring; FADI, Foot & Ankle Disability Index; FAOS, foot and ankle outcome score; FFI, Foot Functional Index; FHSQ, Foot Health Status Questionnaire; L-PRP, leukocyte-platelet—rich plasma; LOE, level of evidence; MRI, magnetic resonance imaging; NR, not reported; P-PRP, pure platelet-rich plasma; PLT, platelet concentration; P-PRP, pure platelet-rich plasma; QOL, quality of life; RCT, randomized controlled trial; ROM, range of motion; SA, sports activities; SANE, Single Assessment Numeric Evaluation; SF-12, Short Form 12; US, ultrasonography; VAS, visual analog scale; VISA, Victorian Institute of Sports Assessment; VISA-A, Victorian Institute of Sports Assessment—Achilles; VISA-P, Victorian Institute of Sports Assessment—Patella; WBC, white blood cell concentration.

positive outcomes were sustained over time. However, this study did not evidence any structural changes as assessed by US.

All case studies but two[55,57] were performed with L-PRP, but the number of injections varied among the studies, with 1 injection,[52,57-59] 2 injections,[53] or 3 injections.[54-56] A significant clinical improvement in both pain and function lasting about 6 to 9 months was reported in all uncontrolled studies. Regarding changes in tendon structure, uncontrolled studies reported a reduction in tendon irregularities (magnetic resonance imaging [MRI] assessment)[55] and reduction of hypoechoic areas as assessed by US.[57]

Achilles Tendon Injuries

Conservative Management. Two randomized clinical trials (1 pilot) have compared PRP with an eccentric loading program versus saline solution injections with an eccentric loading program.[60-62] As expected, the pilot randomized study confirmed feasibility but was underpowered (10 patients per group) and thus was not able to show efficacy.[59,60] The completed randomized clinical trial, involving 27 patients per group, showed nonsuperiority of buffered L-PRP plus eccentric exercises over saline solution plus eccentric exercises.[61] Eccentric exercise therapy is an effective treatment for Achilles tendinopathy; thus, 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 that may necessitate operative intervention once conservative treatments have been exhausted. What is more, the authors did not find any tendon change in vascularity or echogenicity, as assessed by US, 12 months after PRP.[61] This is in sharp contrast to the case series of tendinopathic Achilles tendons (recalcitrant to conservative treatments), in which 2 US-guided injections along with extensive scarification were effective in reducing pain, enhancing function, and improving the structure of the tendon as assessed by US.[66,67] We may infer that more than 1 injection is necessary to recover a degenerated tissue and that a single PRP injection is insufficient to reduce symptoms and modify tendon structure. Most Achilles tendons (81%) were managed with a single injection of 3 to 4 mL of L-PRP (platelet enrichment 4× to 8×).

Still, the results remain controversial because of the scarcity of Level I evidence in this condition. Even though clinical and structural improvement was reported in uncontrolled studies with more than 1 PRP injection, this was not corroborated after 1 single injection. Moreover, as reviewed recently,[84] the literature surrounding other injectable treatments for noninsertional Achilles tendinopathy is of low quality and has shown variable results. Currently, PRP cannot be recommended for Achilles tendinopathy given substantial knowledge deficits such as the number of doses, the procedure of application, and the best PRP formulation that fits the demand of the host tissue.

Surgical Management. Complete Achilles tendon tears are treated surgically. Two controlled studies have examined the efficacy of PRP in the open surgical reconstruction of complete tears.[69,70] Schepull et al.[70] did not find any improvement in the mechanical properties of the Achilles tendon (elasticity modulus and heel rise) operated on with PRP; instead, they found better mechanical behavior of the untreated tendons. Outcomes as evaluated by the elasticity modulus and heel raise were inferior in the PRP group, and function had not been restored 12 months after surgery in either group, although disability did not limit patients in everyday activities. In contrast, Sánchez et al.[69] found decreased cross-sectional areas in PRP-treated groups, pointing to more physiological healing, along with a faster return to sporting activities. The differences between these 2 studies could be attributed to the demographic characteristics of the patients (age [younger in the study of Sánchez et al.] or level of sports activities), the surgical technique, and/or the postoperative rehabilitation protocols. In addition, there were differences in the formulation (pure PRP *v* L-PRP) and in the application protocol.

Plantar Fasciopathy

We have included plantar fasciitis because, as in tendons, the fibroblast is the primary cell in the fascia and the biological concept for PRP application (i.e., cell activator and modulator of inflammation) is the same. There were 4 controlled studies with corticosteroids,[25,74-76] 1 controlled study with dextrose prolotherapy,[77] and 6 uncontrolled studies.[78-83] One randomized controlled study found significant differences between L-PRP and corticosteroids at 6 weeks[25]; positive results have been confirmed after longer follow-up periods.[74] However, Akşahin et al.[76] conducted a study that failed to show a difference in efficacy at 3 weeks and 6 months after treatment. PRP was superior to dextrose prolotherapy in a randomized single-blind trial but did not reach statistical significance: PRP, 9 patients (at final follow-up), versus dextrose prolotherapy, 10 patients.[77] Ongoing clinical trials controlled with corticosteroids should provide more information about the efficacy of L-PRP (GPS III, Biomet Biologics Inc., Warsaw, IN) (NCT00758641) and pure PRP (ACP; Arthrex) (NCT01614223).

Muscle Injuries

Acceleration of muscle repair is especially relevant in elite and professional athletes because of public

attention and economic repercussions. Our search identified 2 randomized controlled studies,[85,86] 2 case-control studies,[87,88] and 2 case series.[89,90] A pioneered controlled study was performed not with PRP but with ACS (i.e., an autologous liquid serum conditioned by incubation of whole blood with glass beads). ACS contains signaling proteins including interleukin (IL) 1b, tumor necrosis factor α, IL-7, fibroblast growth factor 2, IL-1 receptor antagonist, hepatocyte growth factor, platelet-derived growth factor AB, transforming growth factor β1, and insulin-like growth factor 1. The comparator was Traumeel (Heel, Albuquerque, NM)/ Actovegin (Nycomed, Zurich, Switzerland) (3:2) (i.e., homeopathic formulation and amino acids). Baseline characteristics were similar in both groups, that is, tear severity of grade 2 with detection of bleeding on MRI. 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. The experimental group returned to competition after 16.6 days whereas the control group took 22.3 days to return, as decided after a strength assessment by standard isokinetic tests. MRI scans taken at 16 days in both groups confirmed that regression of the edema/ bleeding was faster in the ACS group. Two randomized clinical trials in patients with hamstring injuries provided contradictory results. Whereas Reurink et al.[85] did not find any difference in the time until patients could resume sporting activities (42 days for both groups), A Hamid et al.[86] reported a mean time of 26.7 ± 7 days in the L-PRP group (combined with rehabilitation) versus 42.5 ± 20.6 days in the group that followed only the rehabilitation program. The treatment in the former study consisted of 2 injections of 3 mL of pure PRP that was compared with placebo injections, whereas the treatment in the latter consisted of a single injection of L-PRP.

Pain outcome and functional recovery assessments, as well as sonoelastography assessments, were performed in 30 consecutive professional athletes randomized to receive a single L-PRP injection or conventional management.[88] In the short-term (7 to 21 days after treatment), athletes in the PRP group presented significant improvements in strength and range of motion, as well as faster disappearance of hypoechoic areas and stiffer tissue on sonoelastography. Although healing was faster in the PRP group, both groups tended to converge at 28 days after treatment.

In a preliminary study with low patient numbers, Rettig et al.[89] examined the effects of PRP injection associated with rehabilitation in the treatment of professional National Football League players and the time to resume competition. They found that the time needed to return to competition was similar in both groups (with and without PRP). PRP injections proved to be safe, and no patient in either group (PRP or control) reported any relapse at follow-up (6 months).

Three weekly injections of PRP were administered to 53 recreational athletes with grade II lesions, who were studied retrospectively.[90] Outcome measurements included pain reduction, return to sports, US imaging, relapse, local infection, or any side effect. The treatment was satisfactory for all patients except 1 in whom relapse occurred after 1 year.

Wetzel et al.[91] retrospectively reviewed 15 patients with 17 proximal hamstring injuries, and 12 injuries that failed conventional treatments were treated with a PRP injection at the muscle origin. These patients showed a significant reduction on a visual analog scale and the Nirschl phase rating scale not found in patients treated with traditional conservative methods.

Discussion

We have synthesized the current clinical research in human tendons and muscles, mainly examining PRP formulations and symptom remission after PRP treatment. Considering the heterogeneity of tendinopathies, we have classified tendon studies according to anatomic locations. Overall, in the literature reviewed, more than 1,000 patients have been treated for tendinopathy (including plantar fasciitis); most research focused on upper limb pathology (i.e., rotator cuff and epicondylitis). An L-PRP formulation was predominantly used for conservative management, whereas a clotted gel form of PRP, named "platelet-rich fibrin matrix," was typically used during arthroscopic management. The use of PRP gel as an aid in arthroscopic repair of the rotator cuff has not met the expectancies raised by in vitro studies. Yet, there is still open debate about the dose and the best protocol for PRFM application in arthroscopy. This therapy may decrease the retear rate, but this remains to be confirmed.[36] Conservative management including injections within the supraspinatus or infiltrations within the subacromial space need further investigation, in particular the number of injections and the protocol for application.

Rotator cuff pathology is challenging, patients are diverse, and different biological interventions or combinations may be indicated for different subgroups. The intrinsic healing potential of the rotator cuff may depend on the surrounding stem cells that, once activated, may drive tendon healing.[14,92-95] As an illustration, bone marrow–stimulating techniques have been assayed in a recent clinical trial[96]; although there were not significant differences in structural integrity, subgroup analysis showed better healing in the microfracture group. As shown in the knee, microfractures could be improved when associated with PRP injections.[97] Thus combined biological interventions intended for stem cell activation may improve current

results. Moreover, in vivo tissue engineering performed by a combination of cells, scaffold, and PRP during surgery has shown promising results.[98]

Lower limb pathology has been less widely investigated, with 7 controlled studies involving 143 patients, in 3 different conditions. In general, most clinical studies showed improvement in pain, function, and patient satisfaction (except for Achilles tendon studies), but the quality of the evidence is low, based on case series with a high risk of bias. However, combined treatments such as skin fibroblasts and PRP may improve current results in selected cases.[7]

PRP injections are deemed to be safe, but we must pay attention to metabolic comorbidities[98,99] because L-PRP injection provoked an exuberant inflammatory reaction in a patient with type 1 diabetes.[100] In addition, unexpected poor results have been reported in 3 patients with recalcitrant patellar tendinopathy referred to a clinic after they had received PRP treatment elsewhere.[101]

There is growing interest in optimizing PRP formulations, that is, platelet and leukocyte counts and the balance between these counts, as well as the ratio with respect to plasma proteins. In particular, there is debate about which factor is pivotal in the formulation. To some extent, this conflict was resolved by the finding that different platelet-leukocyte ratios showed a plateau effect of platelet concentrations, with increasing platelet concentrations being detrimental to extracellular matrix synthesis.[102] Increasing the platelet concentration within L-PRP preparations results in the delivery of more anabolic growth factors and decreased proinflammatory cytokines, but the biological effect on tendons is diminished metabolism as indicated by a decrease in the synthesis of both *COL1A1* and *COL3A1*. Together, this information suggests that minimizing leukocytes in PRP is more important than maximizing platelet numbers with respect to decreasing inflammation and enhancing anabolic signaling.

The self-healing potential of skeletal muscle is considerably higher than that of tendon, in part attributed to extensive tissue turnover, as well as substantial innervation and vascularization.[103] The fact that the World Anti-Doping Agency has allowed free therapeutic use of PRP since 2011 prompted several case studies in professional athletes. In the past several years, 3 case series and a controlled study have been published.[87-90] The quality of PRP research in muscle injuries has improved with the recent publication of 2 randomized trials in hamstring injuries, with contradictory results that could be attributed to the comparison group and/or the PRP formulation and application protocol.[83,85,104]

Enhancement of muscle repair by PRP is endorsed by new experimental data regarding promotion of satellite cell proliferation[105] and differentiation with PRP. Furthermore, reinnervation of muscle is crucial to functional recovery of muscle injuries. Sensory improvement after intraneural or perineural injection of PRP has been reported in peroneal nerve palsy and in leprosy peripheral neuropathy.[106,107] In addition, molecular mechanisms underlying the antinociceptive activity of PRP by triggering the production of analgesic mediators such as endocannabinoids have been shown in vivo and in vitro.[108] Taken together, all these studies evidence advancement in PRP science. However, optimization of treatment procedures grounded in sound experimental research data is of utmost importance to profit from this technology.

Given the heterogeneity in tendons and tendinopathies, currently, we are not ready to decide whether PRP therapies are useful or not. Tendons in the upper and lower limbs may have different biochemical and physiological behaviors, and this may explain the discrepancies in response to PRP administration between tendons, as well as the importance of activating cells in the paratenon to enhance healing capabilities. Despite greater costs, increasing the number of interventions may be crucial to achieve tendon regeneration.[109,110]

Limitations

There are several limitations of our review. First, we have provided a comprehensive description of current literature to obtain a broad picture of clinical research in tendon pathology, fasciopathy, and muscle injuries to identify major weaknesses; we did not intend to perform any quantitative synthesis of current data. Second, we have not evaluated the methodologic quality of the included studies; rather, we assigned a level of evidence based on study design and available data in the literature. Lastly, PRPs are described as pure PRP or L-PRP, but we could not capture full differences between intra—pure PRP and intra—L-PRP formulations because of a lack of sufficient description in most studies.

Realistically, a substantial amount of research is still necessary to bring PRP therapies into conservative management of muscle injuries and tendinopathies because findings indicating potential benefit are controversial, given the heterogeneity in formulations and application protocols. Although it needs further confirmation, the clinical evidence suggests that rotator cuff arthroscopy augmentation with PRFM does not provide clinical benefits whereas local injection of PRP may be beneficial to patients with chronic epicondylitis, patellar tendinopathy, Achilles tendinopathy, and plantar fasciitis refractory to other nonsurgical treatments. However, data are insufficient, and the need to optimize protocols is clear, obtaining reliable data on effectiveness parameters from clinical trials and routine pragmatic data.

Conclusions

Given the heterogeneity in tendons and tendinopathies, currently, we are not able to decide whether PRP therapies are useful. Despite advances in PRP science, data are insufficient and there is a clear need to optimize protocols and obtain more high-quality clinical data in both tendinopathies and muscle injuries before making treatment recommendations.

References

1. Loppini M, Maffulli N. Conservative management of tendinopathy: An evidence-based approach. *Muscles Ligaments Tendons J* 2011;1:134-137.
2. Andia I, Sánchez M, Maffulli N. Tendon healing and platelet rich plasma therapies. *Expert Opin Biol Ther* 2010;10:1415-1426.
3. Sharma P, Maffulli N. Tendon injury and tendinopathy: Healing and repair. *J Bone Joint Surg Am* 2005;87:187-202.
4. Ahmad Z, Wardale J, Brooks R, Henson F, Noorani A, Rushton N. Exploring the application of stem cells in tendon repair and regeneration. *Arthroscopy* 2012;28:1018-1029.
5. Connell D, Datir A, Alyas F, Curtis M. Treatment of lateral epicondylitis using skin-derived tenocyte-like cells. *Br J Sports Med* 2009;43:293-298.
6. Clarke AW, Alyas F, Morris T, Robertson CJ, Bell J, Connell DA. Skin-derived tenocyte-like cells for the treatment of patellar tendinopathy. *Am J Sports Med* 2011;39:614-623.
7. Obaid H, Clarke A, Rosenfeld P, Leach C, Connell D. Skin-derived fibroblasts for the treatment of refractory Achilles tendinosis: Preliminary short-term results. *J Bone Joint Surg Am* 2012;94:193-200.
8. Ellera Gomes JL, da Silva RC, Silla LM, Abreu MR, Pellanda R. Conventional rotator cuff repair complemented by the aid of mononuclear autologous stem cells. *Knee Surg Sports Traumatol Arthrosc* 2012;20:373-377.
9. Schnabel LV, Mohammed HO, Miller BJ, et al. Platelet rich plasma (PRP) enhances anabolic gene expression patterns in flexor digitorum superficialis tendons. *J Orthop Res* 2007;25:230-240.
10. de Mos M, van der Windt AE, Jahr H, et al. Can platelet-rich plasma enhance tendon repair? A cell culture study. *Am J Sports Med* 2008;36:1171-1178.
11. Tohidnezhad M, Varoga D, Wruck CJ, et al. Platelet-released growth factors can accelerate tenocyte proliferation and activate the anti-oxidant response element. *Histochem Cell Biol* 2011;135:453-460.
12. Zhang J, Middleton KK, Fu FH, Im HJ, Wang JH. HGF mediates the anti-inflammatory effects of PRP on injured tendons. *PLoS One* 2013;8:e67303.
13. Lane JG, Healey RM, Chase DC, Amiel D. Use of platelet-rich plasma to enhance tendon function and cellularity. *Am J Orthop (Belle Mead NJ)* 2013;42:209-214.
14. Sadoghi P, Lohberger B, Aigner B, et al. Effect of platelet-rich plasma on the biologic activity of the human rotator-cuff fibroblasts: A controlled in vitro study. *J Orthop Res* 2013;31:1249-1253.
15. Bi Y, Ehirchiou D, Kilts TM, et al. Identification of tendon stem/progenitor cells and the role of the extracellular matrix in their niche. *Nat Med* 2007;13:1219-1227.
16. Chen L, Dong SW, Tao X, Liu JP, Tang KL, Xu JZ. Autologous platelet-rich clot releasate stimulates proliferation and inhibits differentiation of adult rat tendon stem cells towards nontenocyte lineages. *J Int Med Res* 2012;40:1399-1409.
17. Chen L, Dong SW, Liu JP, Tao X, Tang KL, Xu JZ. Synergy of tendon stem cells and platelet-rich plasma in tendon healing. *J Orthop Res* 2012;30:991-997.
18. Zhang J, Wang JH. Platelet-rich plasma releasate promotes differentiation of tendon stem cells into active tenocytes. *Am J Sports Med* 2010;38:2477-2486.
19. Heinemeier KM, Schjerling P, Heinemeier J, Magnusson SP, Kjaer M. Lack of tissue renewal in human adult Achilles tendon is revealed by nuclear bomb (14)C. *FASEB J* 2013;27:2074-2079.
20. Andia I, Sánchez M, Maffulli N. Platelet rich plasma therapies for sports muscle injuries: Any evidence behind clinical practice? *Expert Opin Biol Ther* 2011;11:509-518.
21. Mazzocca AD, McCarthy MB, Chowaniec DM, et al. The positive effects of different platelet-rich plasma methods on human muscle, bone, and tendon cells. *Am J Sports Med* 2012;40:1742-1749.
22. Raeissadat SA, Rayegani SM, Hassanabadi H, Rahimi R, Sedighipour L, Rostami K. Is platelet-rich plasma superior to whole blood in the management of chronic tennis elbow: One year randomized clinical trial. *BMC Sports Sci Med Rehabil* 2014;6:12.
23. Krogh TP, Fredberg U, Stengaard-Pedersen K, Christensen R, Jensen P, Ellingsen T. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: A randomized, double-blind, placebo-controlled trial. *Am J Sports Med* 2013;41:625-635.
24. Mishra AK, Skrepnik NV, Edwards SG, et al. Efficacy of platelet-rich plasma for chronic tennis elbow: A double-blind, prospective, multicenter, randomized controlled trial of 230 patients. *Am J Sports Med* 2014;42:463-471.
25. Omar Aziza S, Maha EI, Amal SA, Mahmoud S. Local injection of autologous platelet rich plasma and corticosteroid in treatment of lateral epicondylitis and plantar fasciitis: Randomized clinical trial. *Egypt Rheumatol* 2012;34:43-49.
26. Creaney L, Walla A, Curtis M, Connell D. Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: A prospective, double-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections. *Br J Sports Med* 2011;45:966-971.
27. Peerbooms JC, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: Platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. *Am J Sports Med* 2010;38:255-262.
28. Gosens T, Peerbooms JC, van Laar W, den Oudsten BL. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: A double-blind randomized controlled trial with 2-year follow-up. *Am J Sports Med* 2011;39:1200-1208.

29. Thanasas C, Papadimitriou G, Charalambidis C, Paraskevopoulos I, Papanikolaou A. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: A randomized controlled clinical trial. *Am J Sports Med* 2011;39:2130-2134.
30. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sports Med* 2006;34:1774-1778.
31. Chaudhury S, de La Lama M, Adler RS, et al. Platelet-rich plasma for the treatment of lateral epicondylitis: Sonographic assessment of tendon morphology and vascularity (pilot study). *Skeletal Radiol* 2013;42:91-97.
32. Hechtman KS, Uribe JW, Botto-vanDemden A, Kiebzak GM. Platelet-rich plasma injection reduces pain in patients with recalcitrant epicondylitis. *Orthopedics* 2011;34:92.
33. Malavolta EA, Gracitelli ME, Ferreira Neto AA, Assunção JH, Bordalo-Rodrigues M, de Camargo OP. Platelet-rich plasma in rotator cuff repair: A prospective randomized study. *Am J Sports Med* 2014;42:2446-2454.
34. Antuña S, Barco R, Martínez Diez JM, Sánchez Márquez JM. Platelet-rich fibrin in arthroscopic repair of massive rotator cuff tears: A prospective randomized pilot clinical trial. *Acta Orthop Belg* 2013;79:25-30.
35. Ruiz-Moneo P, Molano-Muñoz J, Prieto E, Algorta J. Plasma rich in growth factors in arthroscopic rotator cuff repair: A randomized, double-blind, controlled clinical trial. *Arthroscopy* 2013;29:2-9.
36. Jo CH, Shin JS, Lee YG, et al. Platelet-rich plasma for arthroscopic repair of large to massive rotator cuff tears: A randomized, single-blind, parallel-group trial. *Am J Sports Med* 2013;41:2240-2248.
37. Weber SC, Kauffman JI, Parise C, Weber SJ, Katz SD. Platelet-rich fibrin matrix in the management of arthroscopic repair of the rotator cuff: A prospective, randomized, double-blinded study. *Am J Sports Med* 2013;41:263-270.
38. Gumina S, Campagna V, Ferrazza G, et al. Use of platelet-leukocyte membrane in arthroscopic repair of large rotator cuff tears: A prospective randomized study. *J Bone Joint Surg Am* 2012;94:1345-1352.
39. Rodeo SA, Delos D, Williams RJ, Adler RS, Pearle A, Warren RF. The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: A prospective, randomized clinical study. *Am J Sports Med* 2012;40:1234-1241.
40. Bergeson AG, Tashjian RZ, Greis PE, Crim J, Stoddard GJ, Burks RT. Effects of platelet-rich fibrin matrix on repair integrity of at-risk rotator cuff tears. *Am J Sports Med* 2012;40:286-293.
41. Jo CH, Kim JE, Yoon KS, et al. Does platelet-rich plasma accelerate recovery after rotator cuff repair? A prospective cohort study. *Am J Sports Med* 2011;39:2082-2090.
42. Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: A prospective RCT study, 2-year follow-up. *J Shoulder Elbow Surg* 2011;20:518-528.
43. Castricini R, Longo UG, De Benedetto M, et al. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: A randomized controlled trial. *Am J Sports Med* 2011;39:258-265.
44. Charousset C, Zaoui A, Bellaïche L, Piterman M. Does autologous leukocyte-platelet-rich plasma improve tendon healing in arthroscopic repair of large or massive rotator cuff tears? *Arthroscopy* 2014;30:428-435.
45. Barber FA, Hrnack SA, Snyder SJ, Hapa O. Rotator cuff repair healing influenced by platelet-rich plasma construct augmentation. *Arthroscopy* 2011;27:1029-1035.
46. Rha DW, Park GY, Kim YK, Kim MT, Lee SC. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: A randomized controlled trial. *Clin Rehabil* 2013;27:113-122.
47. Kesikburun S, Tan AK, Yilmaz B, Yaşar E, Yazicioğlu K. Platelet-rich plasma injections in the treatment of chronic rotator cuff tendinopathy: A randomized controlled trial with 1-year follow-up. *Am J Sports Med* 2013;41:2609-2616.
48. Scarpone M, Rabago D, Snell E, et al. Effectiveness of platelet-rich plasma injection for rotator cuff tendinopathy: A prospective open-label study. *Glob Adv Health Med* 2013;2:26-31.
49. Andia I, Latorre PM, Gomez MC, Burgos-Alonso N, Abate M, Maffulli N. Platelet-rich plasma in the conservative treatment of painful tendinopathy: A systematic review and meta-analysis of controlled studies. *Br Med Bull* 2014;110:99-115.
50. Martin JI, Merino J, Atilano L, et al. Platelet-rich plasma (PRP) in chronic epicondylitis: Study protocol for a randomized controlled trial. *Trials* 2013;14:410.
51. Chahal J, Van Thiel GS, Mall N, et al. The role of platelet-rich plasma in arthroscopic rotator cuff repair: A systematic review with quantitative synthesis. *Arthroscopy* 2012;28:1718-1727.
52. Dragoo JL, Wasterlain AS, Braun HJ, Nead KT. Platelet-rich plasma as a treatment for patellar tendinopathy: A double-blind, randomized controlled trial. *Am J Sports Med* 2014;42:610-618.
53. Vetrano M, Castorina A, Vulpiani MC, Baldini R, Pavan A, Ferretti A. Platelet-rich plasma versus focused shock waves in the treatment of jumper's knee in athletes. *Am J Sports Med* 2013;41:795-803.
54. Filardo G, Kon E, Della Villa S, Vincentelli F, Fornasari PM, Marcacci M. Use of platelet-rich plasma for the treatment of refractory jumper's knee. *Int Orthop* 2010;34:909-915.
55. Charousset C, Zaoui A, Ballaiche L, Bouyer B. Are multiple platelet rich plasma injections useful for treatment of chronic patellar tendinopathy in athletes? A prospective study. *Am J Sports Med* 2014;42:1583-1589.
56. Filardo G, Kon E, Di Matteo B, Pelotti P, Di Martino A, Marcacci M. Platelet-rich plasma for the treatment of patellar tendinopathy: Clinical and imaging findings at medium-term follow-up. *Int Orthop* 2013;37:1583-1589.
57. van Ark M, van den Akker-Scheek I, Meijer LT, Zwerver J. An exercise-based physical therapy program for patients with patellar tendinopathy after platelet-rich plasma injection. *Phys Ther Sport* 2013;14:124-130.
58. Gosens T, Den Oudsten BL, Fievez E, van't Spijker P, Fievez A. Pain and activity levels before and after platelet-rich plasma injection treatment of patellar

tendinopathy: A prospective cohort study and the influence of previous treatments. *Int Orthop* 2012;36:1941-1946.
59. Volpi P, Marinoni L, Bait C, De Girolamo L, Schoenhuber H. Treatment of chronic patellar tendinosis with buffered platelet rich plasma: A preliminary study. *Med Sport* 2007;60:595-603.
60. Kearney RS, Parsons N, Costa ML. Achilles tendinopathy management: A pilot randomised controlled trial comparing platelet-rich plasma injection with an eccentric loading programme. *Bone Joint Res* 2013;2:227-232.
61. de Vos RJ, Weir A, van Schie HT, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: A randomized controlled trial. *JAMA* 2010;303:144-149.
62. de Jonge S, de Vos RJ, Weir A, et al. One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: A double-blind randomized placebo-controlled trial. *Am J Sports Med* 2011;39:1623-1629.
63. Murawski CD, Smyth NA, Newman H, Kennedy JG. A single platelet-rich plasma injection for chronic mid-substance Achilles tendinopathy: A retrospective preliminary analysis. *Foot Ankle Spec* 2014;7:372-376.
64. Filardo G, Kon E, Di Matteo B, et al. Platelet-rich plasma injections for the treatment of refractory Achilles tendinopathy: Results at 4 years. *Blood Transfus* 2014;12:533-540.
65. Kaniki N, Willits K, Mohtadi NG, Fung V, Bryant D. A retrospective comparative study with historical control to determine the effectiveness of platelet-rich plasma as part of nonoperative treatment of acute Achilles tendon rupture. *Arthroscopy* 2014;30:1139-1145.
66. Deans VM, Miller A, Ramos J. A prospective series of patients with chronic Achilles tendinopathy treated with autologous-conditioned plasma injections combined with exercise and therapeutic ultrasonography. *J Foot Ankle Surg* 2012;51:706-710.
67. Gaweda K, Tarczynska M, Krzyzanowski W. Treatment of Achilles tendinopathy with platelet-rich plasma. *Int J Sports Med* 2010;31:577-583.
68. Monto RR. Platelet rich plasma treatment for chronic Achilles tendinosis. *Foot Ankle Int* 2012;33:379-385.
69. Sánchez M, Anitua E, Azofra J, Andía I, Padilla S, Mujika I. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. *Am J Sports Med* 2007;35:245-251.
70. Schepull T, Kvist J, Norrman H, Trinks M, Berlin G, Aspenberg P. Autologous platelets have no effect on the healing of human Achilles tendon ruptures: A randomized single-blind study. *Am J Sports Med* 2011;39:38-47.
71. Ferrero G, Fabbro E, Orlandi D, et al. Ultrasound-guided injection of platelet-rich plasma in chronic Achilles tendinopathy. *J Ultrasound* 2012;15:260-266.
72. Volpi P, Quaglia A, Schoenhuber H, et al. Growth factors in the management of sport-induced tendinopathies: Results after 24 months from treatment. A pilot study. *J Sports Med Phys Fitness* 2010;50:494-500.
73. Finnoff JT, Fowler SP, Lai JK, et al. Treatment of chronic tendinopathy with ultrasound-guided needle tenotomy and platelet-rich plasma injection. *PM R* 2011;3:900-911.
74. Monto RR. Platelet-rich plasma efficacy versus corticosteroid injection treatment for chronic severe plantar fasciitis. *Foot Ankle Int* 2014;35:313-318.
75. Shetty VD, Dhillon M, Hegde C, Jagtap P, Shetty S. A study to compare the efficacy of corticosteroid therapy with platelet-rich plasma therapy in recalcitrant plantar fasciitis: A preliminary report. *Foot Ankle Surg* 2014;20:10-13.
76. Akşahin E, Doğruyol D, Yüksel HY, et al. The comparison of the effect of corticosteroids and platelet-rich plasma (PRP) for the treatment of plantar fasciitis. *Arch Orthop Trauma Surg* 2012;132:781-785.
77. Kim E, Lee JH. Autologous platelet-rich plasma versus dextrose prolotherapy for the treatment of chronic recalcitrant plantar fasciitis. *PM R* 2013;6:152-158.
78. Wilson JJ, Lee KS, Miller AT, Wang S. Platelet-rich plasma for the treatment of chronic plantar fasciopathy in adults: A case series. *Foot Ankle Spec* 2014;7:61-67.
79. Martinelli N, Marinozzi A, Carnì S, Trovato U, Bianchi A, Denaro V. Platelet-rich plasma injections for chronic plantar fasciitis. *Int Orthop* 2013;37:839-842.
80. Kumar V, Millar T, Murphy PN, Clough T. The treatment of intractable plantar fasciitis with platelet-rich plasma injection. *Foot (Edinb)* 2013;23:74-77.
81. O'Malley MJ, Vosseller JT, Gu Y. Successful use of platelet-rich plasma for chronic plantar fasciitis. *HSS J* 2013;9:129-133.
82. Ragab EM, Othman AM. Platelets rich plasma for treatment of chronic plantar fasciitis. *Arch Orthop Trauma Surg* 2012;132:1065-1070.
83. Barret SL, Erredge SE. Growth factors for chronic plantar fasciitis. *Podiatry Today* 2004;17:36-42.
84. Gross CE, Hsu AR, Chahal J, Holmes GB Jr. Injectable treatments for noninsertional Achilles tendinosis: A systematic review. *Foot Ankle Int* 2013;34:619-628.
85. Reurink G, Goudswaard GT, Moen MH, et al. Platelet rich plasma injections in acute muscle injury. *N Engl J Med* 2014;370:2546-2547.
86. A Hamid MS, Mohamed Ali MR, Yusof A, George J, Lee LP. Platelet-rich plasma injections for the treatment of hamstring injuries: A randomized controlled trial. *Am J Sports Med* 2014;42:2410-2418.
87. Wright-Carpenter T, Klein P, Schaferhoff P, Appell HJ, Mir LM, Wehling P. Treatment of muscle injuries by local administration of autologous conditioned serum: A pilot study on sportsmen with muscle strains. *Int J Sports Med* 2004;25:588-593.
88. Bubnov R, Yevseenko V, Semeniv I. Ultrasound guided injections of platelets rich plasma for muscle injury in professional athletes. Comparative study. *Med Ultrason* 2013;15:101-105.
89. Rettig AC, Meyer S, Bhadra AK. Platelet-rich plasma in addition to rehabilitation for acute hamstring injuries in NFL players. Clinical effects and time to return to play. *Orthop J Sports Med* 2013;1:2325967113494354.
90. Bernuzzi G, Petraglia F, Pedrini MF, et al. Use of platelet-rich plasma in the care of sports injuries: Our experience with ultrasound-guided injection. *Blood Transfus* 2013;3:1-6.

91. Wetzel RJ, Patel RM, Terry MA. Platelet-rich plasma as an effective treatment for proximal hamstring injuries. *Orthopedics* 2013;36:e64-e70.
92. Jo CH, Kim JE, Yoon KS, Shin S. Platelet-rich plasma stimulates cell proliferation and enhances matrix gene expression and synthesis in tenocytes from human rotator cuff tendons with degenerative tears. *Am J Sports Med* 2012;40:1035-1045.
93. Song N, Armstrong AD, Li F, Ouyang H, Niyibizi C. Multipotent mesenchymal stem cells from human subacromial bursa: Potential for cell based tendon tissue engineering. *Tissue Eng Part A* 2014;20:239-249.
94. Kida Y, Morihara T, Matsuda K, et al. Bone marrow-derived cells from the footprint infiltrate into the repaired rotator cuff. *J Shoulder Elbow Surg* 2013;22:197-205.
95. Utsunomiya H, Uchida S, Sekiya I, Sakai A, Moridera K, Nakamura T. Isolation and characterization of human mesenchymal stem cells derived from shoulder tissues involved in rotator cuff tears. *Am J Sports Med* 2013;41:657-668.
96. Milano G, Saccomanno MF, Careri S, Taccardo G, De Vitis R, Fabbriciani C. Efficacy of marrow-stimulating technique in arthroscopic rotator cuff repair: A prospective randomized study. *Arthroscopy* 2013;29:802-810.
97. Milano G, Deriu L, Sanna Passino E, et al. Repeated platelet concentrate injections enhance reparative response of microfractures in the treatment of chondral defects of the knee: An experimental study in an animal model. *Arthroscopy* 2012;28:688-701.
98. Protzman NM, Stopyra GA, Hoffman JK. Biologically enhanced healing of the human rotator cuff: 8-month postoperative histological evaluation. *Orthopedics* 2013;36:38-41.
99. Abate M, Schiavone C, Salini V, Andia I. Occurrence of tendon pathologies in metabolic disorders. *Rheumatology (Oxford)* 2013;52:599-608.
100. Kaux JF, Croisier JL, Léonard P, Le Goff C, Crielaard JM. Exuberant inflammatory reaction as a side effect of platelet-rich plasma injection in treating one case of tendinopathy. *Clin J Sport Med* 2014;24:150-152.
101. Bowman KF Jr, Muller B, Middleton K, Fink C, Harner CD, Fu FH. Progression of patellar tendinitis following treatment with platelet-rich plasma: Case reports. *Knee Surg Sports Traumatol Arthrosc* 2013;21:2035-2039.
102. Boswell SG, Schnabel LV, Mohammed HO, Sundman EA, Minas T, Fortier LA. Increasing platelet concentrations in leukocyte-reduced platelet-rich plasma decrease collagen gene synthesis in tendons. *Am J Sports Med* 2014;42:42-49.
103. Andia I, Maffulli N. Platelet-rich plasma for muscle injury and tendinopathy. *Sports Med Arthrosc* 2013;21:191-198.
104. Hamid MS, Mohamed Ali MR, Yusof A, George J. Platelet-rich plasma (PRP): An adjuvant to hasten hamstring muscle recovery. A randomized controlled trial protocol (ISCRTN66528592). *BMC Musculoskelet Disord* 2012;13:138.
105. Li H, Usas A, Poddar M, et al. Platelet-rich plasma promotes the proliferation of human muscle derived progenitor cells and maintains their stemness. *PLoS One* 2013;8:e64923.
106. Sanchez M, Yoshioka T, Ortega M, et al. Ultrasound-guided platelet-rich plasma injections for the treatment of common peroneal nerve palsy associated with multiple ligament injuries of the knee. *Knee Surg Sports Traumatol Arthrosc* 2014;22:1084-1089.
107. Anjayani S, Wirohadidjojo YW, Adam AM, Suwandi D, Seweng A, Amiruddin MD. Sensory improvement of leprosy peripheral neuropathy in patients treated with perineural injection of platelet-rich plasma. *Int J Dermatol* 2014;53:109-113.
108. Brantl SA, Khandoga AL, Siess W. Mechanism of platelet activation induced by endocannabinoids in blood and plasma. *Platelets* 2014;25:151-161.
109. Dallaudière B, Meyer P, Hummel V, et al. Efficacy of second intra-tendinous platelet-rich-plasma injection in case of incomplete response of the first injection: Three-year follow up experience. *Diagn Interv Imaging* 2013;94:871-877.
110. Mautner K, Colberg RE, Malanga G, et al. Outcomes after ultrasound-guided platelet-rich plasma injections for chronic tendinopathy: A multicenter, retrospective review. *PM R* 2013;5:169-175.