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THE EFFECTS OF PLATELET-RICH PLASMA IN CONJUNCTION WITH REHABILITATION FOR LOWER EXTREMITY MUSCULOSKELETAL PATHOLOGIES: A SYSTEMATIC REVIEW WITH META-ANALYSIS

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Abstract

Background: Platelet-rich plasma (PRP) has been considered for its role in facilitating the body's own healing processes, with the potential to complement rehabilitation in the management of lower extremity musculoskeletal pathologies.

Methods: Eligible studies were randomized clinical trials and quasi-experimental trials with completed data analysis; published in English; recruited participants aged >18 years; had at least two groups, with one intervention group receiving PRP injection alone or PRP injection and rehabilitation, and the comparison group receiving either rehabilitation alone or a control group receiving saline and rehabilitation; included at least one outcome measure of pain, disability, quality of life, or return to play. An electronic search was conducted using PubMed, Embase, Cochrane, Pedro, and clinicaltrials.gov. Methodological quality was assessed using the Cochrane Collaboration Risk of Bias (RoB) tool. The Grading of Recommendations Assessment, Development, and Evaluation approach was used to assess the quality of evidence. Meta-analyses were conducted across outcomes in each pathology when possible.

Results: Twenty-one studies assessed Achilles rupture, Achilles tendinopathy, lateral ankle sprain, high ankle sprain, hamstring injury, knee osteoarthritis, acute muscle injury, patellar tendinopathy, and plantar fasciitis, with an average RoB score of 9.9 out of 12. Meta-analyses for Achilles rupture (n = 270) revealed a nonsignificant effect on disability in the short and long term (high level of evidence) when comparing PRP, immobilization, and exercise/physical therapy to placebo, immobilization, and exercise/physical therapy. Meta-analyses for Achilles tendinopathy revealed a nonsignificant effect on pain (n = 64) in the short term, and disability in the short (n = 138) as well as long term (n = 192) (very low to low level of evidence) when comparing PRP and exercise to placebo and exercise.

Conclusions: While individual studies demonstrated significant findings across outcomes, the non-significant pooled results and inability to perform further meta-analyses made it difficult to provide definitive recommendations for the addition of PRP to exercise for lower extremity musculoskeletal pathologies. Future studies should standardized PRP exercise rehabilitation protocols with better dosage parameters, consider larger sample sizes, and have short and long term follow-up periods consistent with the Cochrane Collaboration.

Keywords: *exercise; platelet-rich plasma; rehabilitation*

BACKGROUND

Musculoskeletal injuries continue to prevail, and are therefore expensive for society.[1-3] With emphasis on the quadruple aim of healthcare (reducing costs, improving population health, patient experience, and healthcare team well-being),[4] physicians and allied healthcare professionals are responsible for providing cost-effective, high-quality care that often involves nonsurgical management of lower extremity (LE) musculoskeletal pathologies (Achilles rupture/tendinopathy, lateral ankle sprain, high ankle sprain, hamstring injury, knee osteoarthritis, acute traumatic muscle injuries, patellar tendinopathy, and plantar fasciitis).[4] Recently regenerative medicine, such as stem cells and platelet-rich plasma (PRP), has gained popularity among the orthopedic, sports medicine, and rehabilitation communities as a safe adjunct to physical therapy, rehabilitation, and exercise with the goal of initiating and augmenting the healing potential of musculoskeletal injuires.[5-8]

Platelet-rich plasma is the most common orthobiologic used and has demonstrated positive effects in the management of musculoskeletal pathologies.[9-11] Recent trends have demonstrated an increase in expenses associated with PRP usage each year, indicating an ease of implementation and an increase in demand for safe, nonsurgical, minimally invasive options.[5] Often, PRP is injected into the injured tissue or region, with the goal of initiating a cascade of local healing responses to facilitate an increase in growth hormone and anti-inflammatory cytokines that are produced as part of the normal healing process.[7,12] Therefore, PRP has been considered in clinical practice for its role in facilitating the body's own healing processes. While there is inconsistency in literature on the dosage, histologic makeup of PRP injections, and patient cohorts potentially to improve with PRP, one consistent theme throughout is its role in treating musculoskeletal pathologies that have been recalcitrant to the normal healing process.[7,13] While a Cochrane Review found insufficient evidence to support the use of PRP as a standalone treatment for soft tissue injuries,[14] clinicians must consider combining PRP injections with other forms of treatment such as exercise/rehabilitation for their complementary effects. PRP injections have the potential to create a healing environment for tissues, in which subsequent loading through exercise may create positive long-term changes with the potential to offset the challenges of treating LE musculoskeletal pathologies.

Patients with sport-related LE musculoskeletal injuries are often a population of particular interest in the orthopedic literature, given challenges with the management of injury as it pertains to time to return to play, high reinjury rate, and difficulties in returning to pre-injury levels of competition. The US Bureau of Labor and Statistics found that from 2011 to 2015, 18% of Americans aged 15 years and older engaged in some form of sport or exercise on a daily basis.[15] The US Center for Disease Control and Prevention (CDC) also reported that 213 million Americans aged 6 years and older participated in sports and fitness activities in 2015, which is an increase from 209 million in 2014.[16] As the rate of participation in sports and exercise at various levels of competition increases, so does the risk for LE musculoskeletal injuries as well as the concern for increased prevalence of comorbid conditions in the environment of a sedentary lifestyle. Therefore, in the absence of evidence-based, standardized return to play criteria, it is imperative that we find innovative ways to maximize tissue healing to return active individuals to optimal levels of sport participation.[17,18]

Numerous studies have been conducted assessing the role of PRP in the management of LE musculoskeletal pathologies.[19-39] These studies are important as they discuss the effect of PRP in comparison to, or in conjunction with, exercise assessing clinically important effects on physical function and return to play timeline. While previous systematic reviews examining the effectiveness of PRP are present, limitations in methodological design, the inability to compare PRP to rehabilitation interventions, and the lack of assessment on return to play have prevented researchers and clinicians from drawing strong conclusions regarding its role in managing patients with LE pathologies. Therefore, the purpose of this systematic review with meta-analysis and formal grading of evidence is to assess the effectiveness of PRP alone or in addition to rehabilitation, compared to rehabilitation alone on pain, disability, and quality of life in patients with LE musculoskeletal pathologies.

METHODS

Protocol and registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[40] (**A**ppendix) and registered in (PROSPERO; #CRD42022313157).

Inclusion criteria

Studies had to meet the following inclusion criteria: (1) randomized clinical trials and quasi-experimental trials with completed data analysis; (2) published in English; (3) recruited participants aged >18 years; (4) had at least two groups with the intervention group receiving PRP injection alone or PRP injection and rehabilitation, and the comparison group receiving either rehabilitation alone or a control group receiving saline and rehabilitation; and (5) included at least one outcome measure of pain, disability, quality of life, or return to play.

Exclusion criteria

Studies were excluded if: (1) they were retrospective studies, or case studies/series; (2) subjects underwent surgical intervention; (3) injection was combined with dry needling or extracorporeal shockwave therapy; (4) PRP was compared to injections other than saline; (5) bone marrow aspirate or adipose grafts were used in conjunction with PRP; and (6) studies did not include physical therapy, rehabilitation, or an exercise program.

Search strategy and study selection

An electronic search was conducted by both authors in February 2022 using PubMed, Embase, Cochrane, Pedro, and clinicaltrials.gov for identifying all relevant articles without restriction of date. Clinicaltrials.gov was included to capture gray literature not published due to nonsignificant findings. The search strategy is given in Table 1. A hand search of reference lists of related articles was also conducted by the second author. Each author examined all titles and abstracts to screen for eligibility. Full-text articles were assessed for the inclusion criteria to determine final eligibility. In case of discrepancy, it was resolved through discussion until a consensus was reached.

Interventions

The intervention of interest in this systematic review was PRP injection. Across included studies, the number of injections and administration techniques vary considerably, with some details provided in Table 2 and more

Table 1. Search Strategy

Database	Search Strategy	Yield
PubMed	((Platelet-rich plasma) OR (PRP) AND (clinicaltrial [Filter] OR randomizedcontrolledtrial [Filter])) AND ((Physical therapy) OR (Rehabilitation) AND (clinicaltrial [Filter] OR randomizedcontrolledtrial [Filter]))	163
	(Platelet-rich plasma OR PRP) AND (Exercise)	78
	(Platelet-rich plasma OR PRP) AND (Physical Therapy OR Rehabilitation OR Exercise) AND Musculoskeletal	77
Cochrane Library	((Platelet-rich plasma) OR (PRP)) AND (physical therapy) OR (rehabilitation) OR (exercise)):kw	54
	((Platelet-rich plasma OR PRP) AND (Physical therapy OR Rehabilitation OR Exercise) AND (Musculoskeletal)):kw	3
Embase	((Platelet-rich plasma) OR (PRP)) AND ((Physical therapy) OR (Rehabilitation) OR (exercise)):kw	23
	((Platelet-rich plasma OR PRP) AND (Physical therapy OR Rehabilitation OR Exercise) AND Musculoskeletal)):kw	3
Pedro	Simple search: platelet-rich plasma	31
	Simple search: PRP	49
Clinicaltrials.gov	Advanced search: platelet-rich plasma, studies with results, interventional studies	32

kw, keyword.

Table 2. Description of Studies

Study	Participants	Intervention	Comparison	Outcomes	Follow-up	Summary of Results
Achilles Rupture						
Boesen et al. 2020[21] RCT	n = 40 0 F, 40 M Age: PRP 39.3 y ± 7.4 y Placebo 41.7 y ± 8.9 y Symptom duration: <4 days	PRP + orthosis + exercise n = 20 • US-guided PRP injection 4 injections, 1 at baseline and subsequent injections at every 2 weeks • Ankle orthosis with three 1.5-cm wedges, fixing the ankle in plantarflexion and gradually brought to neutral with removal of wedge every at 2 weeks; 8 weeks total • Standard heel cap shoes with 1-cm elevation For 4 weeks after removal of orthosis • Full weight-bearing permitted after application of orthosis • HEP: mobility, balance, plantar flexor function, strength Starts week 9	Placebo + orthosis + exercise n = 20 • US-guided saline injection 4 injections, 1 at baseline and subsequent injections at every 2 weeks • Ankle orthosis with three 1.5-cm wedges, fixing the ankle in plantarflexion and gradually brought to neutral with removal of wedge every at 2 weeks; 8 weeks total • Standard heel cap shoes with 1-cm elevation For 4 weeks after removal of orthosis • Full weight-bearing permitted after application of orthosis • HEP: mobility, balance, plantar flexor function, strength Starts week 9	ATRS Heel rise work Heel rise height	8 weeks 3 months 6 months 9 months 12 months	Not statistically significant between group differences Both groups demonstrated statistically significant improvement in ATRS, heel rise work, and heel rise height
Keene et al. 2019[32] RCT	n = 230 57 F, 173 M Age: PRP 45.9 y ± 13.7 y Placebo 45.2 y ± 12.4 y Symptoms duration: PRP 5.4 d ± 2.9 d Placebo 5.2 d ± 3.1 d	PRP + immobilization + PT n = 114 • PRP injection into Achilles tendon gap 1 injection • Ankle immobilization in equinus position At least for 3 weeks, but no NWB or full-time immobilization for longer than 6 weeks • Rehabilitation program supervised by physical therapist 24 weeks (unclear)	Placebo + immobilization + PT n = 116 • Dry needle inserted with empty syringe into Achilles tendon gap 1 injection • Ankle immobilization in equinus position At least for 3 weeks, but no NWB or full-time immobilization for longer than 6 weeks • Rehabilitation program supervised by physical therapist 24 weeks (unclear)	VAS ATRS Heel rise endurance test SF-36	4 weeks 7 weeks 13 weeks 24 weeks	Not statistically significant between group differences

(*Continues*)

Table 2. (Continued)

Study	Participants	Intervention	Comparison	Outcomes	Follow-up	Summary of Results
Boesen et al. 2017[22] RCT	n = 60 0 F, 60 M Age: PRP 43.1 y ± 8.1 y Placebo 40.9 y ± 6.6 y Symptoms duration: PRP 27.0 wks ± 34.0 wks Placebo 30.8 wks ± 37.4 wks	PRP + eccentric loading n = 20 • US-guided PRP injection between Achilles tendon and peritendinous tissue 4 injections, 1 at baseline and subsequent injections at every 2 weeks • Alfredson protocol: 2x/day, 180 repetitions per day 12 weeks, started 2 days after each injection	Placebo + eccentric loading n = 20 • US-guided saline injection between Achilles tendon and peritendinous tissue 4 injections, 1 at baseline and subsequent injections every 2 weeks • Alfredson protocol: 2x/day, 180 repetitions per day 12 weeks, started 2 days after each injection	VAS VISA-A Heel rise test	6 weeks 12 weeks 24 weeks	Statistically significant between group differences in VAS and VISA-A favoring PRP, but not heel rise test Both groups demonstrated statistically significant improvement in VISA-A, VAS, and heel rise test
de Jonge et al. 2011[25] RCT	n = 54 Age, mean (range): 49.7 y (26–70 y) Symptoms duration, mean; median (range): 62.6 wks; 32.0 wks (8–520 wks)	PRP + eccentric loading n = 27 • US-guided PRP injection 1 injection • No sports activity for 4 weeks • Stretching program started 2 weeks after injection • Alfredson protocol: 2x/day, 180 repetitions per day 12 weeks, started 4 weeks after injection	Placebo + eccentric loading n = 27 • US-guided saline injection 1 injection • No sports activity for 4 weeks • Stretching program started 2 weeks after injection • Alfredson protocol: 2x/day, 180 repetitions per day 12 weeks, started 4 weeks after injection	VISA-A	6 weeks 12 weeks 24 weeks 1 year	Not statistically significant between group differences Both groups demonstrated statistically significant improvement in VISA-A
de Vos et al. 2010[26] RCT	n = 54 28 F, 26 M Age: PRP 49.0 y ± 8.1 y Placebo 50.0 y ± 9.4 y Symptoms duration, median (range): PRP 36 wks (24–78 wks) Placebo 26 wks (16–104 wks)	PRP + eccentric loading n = 27 • US-guided PRP injection 1 injection • Only short-distance walking for 48 h after injection • Walking up to 30 min allowed, days 3–7 after injection • Stretching program started 1 week after injection • Alfredson protocol: 2x/day, 180 repetitions per day 12 weeks, started 2 weeks after injection	Placebo + eccentric loading n = 27 • US-guided saline injection 1 injection • Only short-distance walking for 48 h after injection • Walking up to 30 min allowed, days 3–7 after injection • Stretching program started 1 week after injection • Alfredson protocol: 2x/day, 180 repetitions per day 12 weeks, started 2 weeks after injection	VISA-A	6 weeks 12 weeks 24 weeks	Not statistically significant between group differences Both groups demonstrated statistically significant improvement in VISA-A

Kearney et al. 2013[31] RCT	n = 20 13 F, 7 M Age, mean (range): PRP 47.8 y (35–59 y) Eccentric 49.9 y (36–66 y) Symptoms duration, mean (range): PRP 30.8 m (9–156 m) Eccentric 28.1 m (8–144 m)	PRP n = 10 • PRP injection into Achilles tendon 1 injection • Advised to gradually return to ADLs and sport	Eccentric loading n = 10 • Instructional manual with Alfredson protocol: 2x/day, 180 repetitions per day 12 weeks	VISA-A EQ-5D EQ-5D VAS	6 weeks 3 months 6 months	Not statistically significant between group differences in VISA-A or EQ-5D Both groups demonstrated statistically significant improvement in VISA-A, but not EQ-5D
Krogh et al. 2016[33] RCT	n = 24 11 F, 13 M Age: PRP 46.7 y ± 9.0 y Placebo 51.8 y ± 9.4 y Symptoms duration: PRP 58.0 m ± 75.6 m Placebo 32.0 m ± 17.2 m	PRP + exercise n = 12 • US-guided PRP injection into thickest part of Achilles tendon 1 injection • Advised to minimize strain on Achilles for 4 days following injection • Home therapy rehabilitation program: eccentric strengthening, stretching, coordination 12 weeks (unclear)	Placebo + exercise n = 12 • US-guided saline injection into thickest part of Achilles tendon 1 injection • Advised to minimize strain on Achilles for 4 days following injection • Home therapy rehabilitation program: eccentric strengthening, stretching, coordination 12 weeks (unclear)	NPRS VISA-A	3 months 6 months 12 months	Not statistically significant between group differences in VISA-A or NPRS
Lateral ankle sprain						
Blanco-Rivera et al. 2019[20] RCT	n = 23 10 F, 13 M Age: PRP 27.9 y ± 12.1 y Control: 25.5 y ± 15.4 y Symptoms duration: <48 h	PRP + immobilization + rehabilitation n = 12 • PRP injection into ATFL 1 injection • Immobilized by below-the-knee plaster cast with foot in neutral Removed after 10 days • Weight-bearing as soon as pain allowed • Rehabilitation program[41]: ROM, isometric and isotonic strengthening, proprioception training, sport-specific activity	Immobilization + rehabilitation n = 11 • Immobilized by below-the-knee plaster cast with foot in neutral Removed after 10 days • Weight-bearing as soon as pain allowed • Rehabilitation program[41]: ROM, isometric and isotonic strengthening, proprioception training, sport-specific activity	VAS AOFAS FADI	3 weeks 5 weeks 8 weeks 24 weeks	Statistically significant between group differences in VAS and AOFAS at 3, 5, and 8 weeks favoring PRP, but not at 24 weeks Statistically significant between group difference in FADI at 8 weeks, but not at 3, 5, or 24 weeks

(*Continues*)

Table 2. (Continued)

Study	Participants	Intervention	Comparison	Outcomes	Follow-up	Summary of Results
High ankle sprain						
Laver et al. 2014[34] RCT	n = 16 Age: PRP 22.6 y ± 4.2 y Control: 22.0 y ± 4.8 y Symptoms duration: NA	PRP + immobilization + PT n = 8 • US-guided PRP injection into syndesmosis at level of AITFL 2 injections, 1 at baseline and another 7 days later • Immobilized in walking boot at 10° of PF, neutral DF after 3 days • NWB for 11 days, progressive WB from 11–13 days, unrestricted WB after 2 weeks • PT protocol: ROM, proprioception, peroneal strengthening, functional rehabilitation No set duration	Immobilization + PT n = 8 • Immobilized in walking boot at 10° of PF, neutral DF after 3 days • NWB for 11 days, progressive WB from 11–13 days, unrestricted WB after 2 weeks • PT protocol: ROM, proprioception, peroneal strengthening, functional rehabilitation No set duration	RTP		Statistically significant between group difference in return to play favoring PRP
Hamstring injury						
Hamid et al. 2014[28] RCT	n = 28 4 F, 24 M Age, median ± IQR: PRP 20.0 y ± 6.5 y Placebo 21.0 y ± 8.5 y Symptoms duration, median ± IQR: PRP 5 d ± 3 d Placebo 5 d ± 3 d	PRP + PT n = 14 • US-guided autologous PRP injection 1 injection • Reduce activities for 48 h • Rehabilitation exercise supervised by sports physical therapist focused on progressive agility and trunk stabilization • HEP Maximum of 16 weeks	PT n = 14 • Reduce activities for 48 h • Rehabilitation exercise supervised by sports physical therapist focused on progressive agility and trunk stabilization • HEP Maximum of 16 weeks	RTP		Statistically significant between group difference in return to play time favoring PRP Not statistically significant between group differences in pain interference scores

Hamilton et al. 2015[29]	n = 90 0 F, 90 M Age: PRP 26.6 y ± 5.9 y PT 25.5 y ± 5.7 y Symptoms duration: PRP 1.8 d ± 0.9 d PT 2.3 d ± 1.1 d	PRP + PT n = 30 • PRP injection into the hamstring muscle belly to depth corresponding to depth of injury 1 injection • PT: six-stage rehabilitation program supervised by physical therapist, including ROM, progressive strengthening, core stability, agility, sports-specific functional field testing 5x/week, started 24 h after injection Duration unclear	PT n = 30 • PT: six-stage rehabilitation program supervised by physical therapist, including ROM, progressive strengthening, core stability, agility, sports-specific functional field testing 5x/week, started 24 h after injection Duration unclear	RTP Reinjury rate	2 months 6 months	Not statistically significant between group differences
Reurink et al. 2014[36] RCT	n = 80 4 F, 76 M Age: PRP 28.0 y ± 7.0 y Placebo 30.0 y ± 8.0 y Symptoms duration, median (IQR): PRP 3 (2–4) Placebo 3 (2–5)	PRP + PT n = 41 • US-guided PRP intramuscular injection 2 injections, 1 within 5 days of injury, and another 5–7 days later • Supervised PT • HEP Duration unclear	Placebo + PT n = 39 • US-guided saline intramuscular injection 2 injections, 1 within 5 days of injury, and another 5–7 days later • Supervised PT • HEP Duration unclear	RTP Reinjury rate	2 months 6 months	Not statistically significant between group differences
Reurink et al. 2015[37] RCT* Same subjects, longer follow-up	n = 80 4 F, 76 M Age: PRP 28.0 y ± 7.0 y Placebo 30.0 y ± 8.0 y Symptoms duration, median (IQR): PRP 3 (2–4) Placebo 3 (2–5)	PRP + PT n = 41 • US-guided PRP intramuscular injection 2 injections, 1 within 5 days of injury, and the other 5–7 days later • Supervised PT • HEP Duration unclear	Placebo + PT n = 39 • US-guided saline intramuscular injection 2 injections, 1 within 5 days of injury, and the other 5–7 days later • Supervised PT • HEP Duration unclear	NPRS Reinjury rate	1 week 4 weeks 10 weeks 26 weeks 1 year	Not statistically significant between group differences

(*Continues*)

Table 2. (Continued)

Study	Participants	Intervention	Comparison	Outcomes	Follow-up	Summary of Results
Knee osteoarthritis						
Angoorani et al. 2015[19] RCT	n = 54 47 F, 7 M Age: PRP 62.15 y ± 12.14 y TENS + EX 61.59 y ± 8.07 y Symptoms duration: NA	PRP n = 27 • PRP intra-knee injections 2 injections, 4 weeks apart	TENS + exercise n = 27 • TENS: 100 hertz × 30 min 10 sessions, 2x/week for 5 weeks • HEP: knee resistance for 3 sets of 10 reps and flexibility for 1 set of 5 reps 5 weeks (unclear)	VAS KOOS: pain, symptoms, ADL, sport/Rec, QOL	4 weeks 8 weeks	Statistically significant between group difference in KOOS symptom score favoring PRP at 4 weeks, but not at 8 weeks Both groups demonstrated statistically significant improvement in VAS at 4 weeks, but not at 8 weeks Statistically significant improvement in KOOS pain, symptoms, and ADL score at 4 weeks for PRP, but only pain for TENS + EX
Elik et al. 2020[27] RCT	n = 60 53 F, 4 M Age: PRP 61.30 y ± 7.91 y Placebo 60.19 y ± 6.80 y Symptoms duration: NA	PRP + exercise n = 30 • PRP injection into the knee 3 injections, 1 week apart • Asked to refrain from activity that could cause pain for 2 days after injection • Exercise program: ROM, stretching of hamstrings, rectus femoris, gastrocnemius, and strengthening of quadriceps femoris 6 months, started after the 3rd injection	Placebo + exercise n = 30 • Saline injection into the knee 1 injection • Asked to refrain from activity that could cause pain for 2 days after injection • Exercise program: ROM, stretching of hamstrings, rectus femoris, gastrocnemius, and strengthening of quadriceps femoris 6 months, started after injection	VAS WOMAC SF-36	1 month 6 months	Statistically significant between group difference in VAS and SF-36 PF at 1 and 6 months, and in WOMAC total score and SF-36 MH at 6 months favoring PRP Both groups demonstrated statistically significant improvement in VAS and WOMAC scores at 1 and 6 months Statistically significant improvement in SF-36 PF and MH at 1 and 6 months for PRP, and in SF-36 PF at 6 months for placebo

Acute muscle injury						
Bubnov et al. 2013[23] RCT	n = 34 0 F, 34 M Age: 24 y Symptoms duration: within 24 h Muscle injury (PRP, PT): thigh trauma 10, 8 Foot and ankle trauma 5, 5 Shoulder trauma 2, 4	PRP + conventional conservative therapy n = 17 • US-guided PRP injection into muscle lesion • Immobilization • PT • Anti-inflammatory therapy 4 weeks	Conventional conservative therapy n = 17 • Immobilization • PT • Anti-inflammatory therapy 4 weeks	VAS ROM Strength	7 days 14 days 21 days 28 days	Statistically significant between group differences in pain relief favoring PRP at 7, 14, and 21 days, but not at 28 days Statistically significant between group differences in strength and ROM favoring PRP at 7 and 14 days, but only ROM at 28 days
Rossi et al. 201638 RCT	n = 75 17 F, 58 M Age: PRP 22.9 y ± 3.5 y PT 21.8 y ± 3.2 y Symptoms duration: PRP 4 d ± 2 d PT 4 d ± 2 d Muscle injury (PRP, PT): Hamstrings 16, 18 Quadriceps 7, 8 Gastroc 12, 11	PRP + PT n = 35 • Intralesional autologous PRP injection 1 injection given 1–4 days after injury • Asked to reduce activity for 24 h • PT: four phases, supervised by physical therapist, progressive agility, trunk stabilization 3x/week for duration of study (until RTP), started 2 days after injection • HEP	PT n = 40 • PT: four phases, supervised by physical therapist, progressive agility, trunk stabilization 3x/week for duration of study (until RTP), started 2 days after injection • HEP	VAS RTP Reinjury rate	2 months 12 months 24 months	Statistically significant between group differences favoring PRP in VAS and RTP, but not reinjury rate Both groups demonstrated statistically significant improvement in VAS

(*Continues*)

Table 2. (Continued)

Study	Participants	Intervention	Comparison	Outcomes	Follow-up	Summary of Results
Patellar tendinopathy						
Scott et al. 201939 RCT	n = 61 5 F, 36 M Age: PRP 32.0 y ± 9.8 y Placebo 31.0 y ± 7.9 y Symptoms duration: PRP 2.2 y ± 1.7 y Placebo 1.8 y ± 1.4 y	PRP + PT n = 20 • US-guided PRP injection into the patellar tendon 1 injection • Instructed to refrain from exercise for 48 h after injection • PT: heavy slow resistance training (concentric and eccentric, as described by Kongsgaard et al. 2009), supervised by physical therapist 3x/week for 6 weeks, started 1 week after injection	Placebo + PT n = 20 • US-guided saline injection into the patellar tendon 1 injection • Instructed to refrain from exercise for 48 h after injection • PT: heavy slow resistance training (concentric and eccentric, as described by Kongsgaard et al. 2009), supervised by physical therapist 3x/week for 6 weeks, started 1 week after injection	NPRS VISA-P	6 weeks 12 weeks 12 months	Not statistically significant between group differences
Plantar fasciitis						
Chew et al. 2013[24] RCT	n = 54 17 F, 18 M Age, median (IQR): ACP 46.0 y (38–51 y) Conventional 47.5 y (41–53 y) Symptoms duration, median (IQR): ACP 12 mo (7–24 m) Conventional 10.5 m (6–16 m)	ACP + conventional treatment n = 19 • US-guided autologous conditioned plasma into plantar fascia at the medial calcaneal tubercle • Orthotics if indicated • HEP: standing lunge stretch of gastrocnemius and soleus, plantar fascia stretch, 3-s × 3 reps per stretch 1–2 sessions for education of HEP performed 3x/day	Conventional treatment n = 16 • Orthotics if indicated • HEP: standing lunge stretch of gastrocnemius and soleus, plantar fascia stretch, 3-s × 3 reps per stretch 1–2 sessions for education of HEP performed 3x/day	VAS AOFAS ankle hind-foot scale	1 month 3 months 6 months	Statistically significant between group differences in VAS at 1 month, and in AOFAS ankle hind-foot scale at 3 and 6 months favoring ACP Both groups demonstrated statistically significant improvement in VAS and AOFAS ankle kind-foot scale

Johnson-Lynn et al. 2018[30] RCT	n = 28 19 F, 9 M Age: PRP 47.9 y ± 10.7 y Placebo 52.1 y ± 10.3 y Symptom duration: >6 m	PRP + immobilization + PT n = 14 • PRP injection into plantar fascia • Immobilization in boot NWB for 2 days, then FWB in boot for 2–3 weeks • PT: standardized 12 months (unclear)	Placebo + immobilization + PT n = 14 • Saline injection into plantar fascia • Immobilization in boot NWB for 2 days, then FWB in boot for 2–3 weeks • PT: standardized 12 months (unclear)	VAS	6 months 12 months	Not statistically significant between group differences in VAS (study lacked power) Both groups demonstrated statistically significant improvement in VAS at 6 months
Mahindra et al. 201635 RCT	n = 75 28 F, 19 M Age: PRP 30.72 y ± 7.42 y Placebo 35.48 y ± 9.54 y Symptom duration: NA	PRP + PT n = 25 • PRP injection to the plantar fascia at the point of maximum tenderness 1 injection • PT: stretching of the plantar fascia and calf muscles 3 weeks (unclear)	Placebo + PT n = 25 • Saline injection to the plantar fascia at the point of maximum tenderness 1 injection • PT: stretching of the plantar fascia and calf muscles 3 weeks (unclear)	VAS AOFAS ankle hind-foot scale	3 weeks 3 months	Statistically significant between group differences in VAS and AOFAS ankle hind-foot scale at 3 weeks and 3 months favoring PRP Statistically significant improvement in VAS and AOFAS ankle hind-foot scale at 3 weeks and 3 months for PRP, but not for placebo

ATRS, Achilles tendon Total Rupture Score; AOFAS, American Orthopaedic Foot & Ankle Society; AITFL, anterior-inferior tibio-fibular ligament; ATFL, anterior talofibular ligament; ACP, autologous conditioned plasma; BPI, Brief Pain Index; BPI-SF, Brief Pain Index-Short Form; DF, dorsiflexion; EQ-5D, EuroQoL-5 dimension; FADI, Foot and Ankle Disability Index; FWB, full weight-bearing; HEP, home exercise program; IQR, interquartile range; KOOS, Knee Injury Osteoarthritis Outcome Score; NWB, non-weight-bearing; NA, not applicable; NPRS, Numeric Pain Rating Scale; PSFS, Patient-Specific Functional Scale; PT, physical therapy; PF, plantarflexion; PRP, platelet-rich plasma; RCT, randomized controlled trial; ROM, range of motion; RTP, return to play; SF-36 MH, Short Form-36 mental health; SF-36 PF, Short Form-36 physical function; TENS, transcutaneous electrical nerve stimulation; US, ultrasound; VISA-A, Victorian Institute of Sport Assessment Questionnaire-Achilles tendon; VISA-P, Victorian Institute of Sport Assessment Questionnaire-Patellar tendon; VAS, Visual Analog Scale; WB, weight-bearing; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

specifics available in the original publications. PRP alone or in conjunction with a comparison intervention was compared to rehabilitation, physical therapy, exercise, immobilization, or a control group that included a placebo (saline) intervention group (Table 2).

Outcomes

Primary outcomes for this review were pain, disability, quality of life, and return to play (Table 3). The heel rise test for work, height, and endurance was included as a secondary outcome measure for Achilles rupture and tendinopathy, with reinjury rate assessed for hamstring and acute muscle injury. Pain was measured using the Visual Analog Scale (VAS; 0–100 mm/0–10 cm) and Numeric Pain Rating Scale (NPRS; 0–10 points). Disability was measured using the following parameters/scales: Achilles Tendon Rupture Score (ATRS; 0–100 points), American Orthopedic Foot & Ankle Society (AOFAS; 0–100%), Foot and Ankle Disability Index (FADI; 0–100%), Knee Injury Osteoarthritis Outcome Score (KOOS; 0–100%), Victorian Institute of Sport Assessment Questionnaire–Achilles & Patellar Tendon (VISA-A, VISA-P; 0–100 points), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; 0–98 points). Quality of life was measured using the EuroQoL-5 Dimension (EQ-5D; 0–100 points) and Short Form-36 (SF-36; 0–100).

Timing of outcome assessment

Outcomes were assessed in both short (<3 months) and long (6–12 months) terms. In case of multiple time points, the one closest to 3-month and 12-month follow-up was used in data analyses, unless all studies had similar follow-up assessments.[62]

Methodological quality

Methodological quality was assessed using the Cochrane Collaboration Risk of Bias (RoB) tool,[62] which examines risk of bias across the following five domains of bias: selection, performance, detection, attrition, and reporting. If the criteria was fulfilled, each item awarded a "Yes" and received a score of 1, and if the criteria was not fulfilled or was unclear, then the item was assigned a "No" or "Unclear," resulting in a score of 0.[62] The sum of the points represented the total risk of bias out of 12 points, with higher scores indicating lower risk of bias. Both authors independently scored each included study, with discrepancies resolved through discussion until consensus was reached (Table 4).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to provide an overall assessment of the quality of evidence across the following five domains: risk of bias, inconsistency of results, indirectness or evidence, imprecision, and publication bias.[62,63] The GRADE approach provided a summary rating of the quality of the body of evidence for the effect of an intervention on a particular outcome measure, providing a recommendation that may guide clinicians' decision-making in selecting the most optimal interventions. Following evidence appraisal, outcomes are classified by the level of evidence (Table 5).

Data collection

Both authors performed data extraction, and included study details and design, patient demographics, interventions, timing of assessment, outcome measures, and results (Table 2). In the event of missing data, study authors were contacted.

Data analysis

Data analysis was conducted using Revman 5.4. Post-test mean values and standard deviations (SD) were used for meta-analysis, unless articles only reported change scores. In case standard deviations were not provided, the authors calculated them for performing meta-analysis. A random-effects model with inverse variance was used to calculate mean differences (MD) for pain and disability when outcomes could be converted to the same numerical scale, or standardized mean differences (SMD) and 95% confidence interval (CI) if conversion to the same numerical scale failed.[62-64] Mean differences were calculated when possible so that minimal clinically important differences (MCID) could be discussed in relation to patient improvement. However, because of the heterogeneity in data reporting, standardized mean differences were required. Statistical heterogeneity was evaluated using the I^2 statistic, with values greater than 50% indicating high heterogeneity.[65] Effect sizes were presented in forest plots and interpreted based on previous research: 0.2

Table 3. Psychometric Properties of Included Outcome Measures

Outcome Measure	Description	Reliability	MDC/MCID
Pain			
Visual Analog Scale (VAS)[42]	Self-reported measure of pain Vertical or horizontal line scaled from 1–100 mm, where 1 represents "no pain" and 100 represents "worst possible pain"	ICC = 0.97	MDC = 8 mm
Numeric Pain Rating Scale[42]	Self-reported measure of pain 11-point scale (0–10), where 0 represents "no pain" and 10 represents "worst pain imaginable"	ICC = 0.95	MDC = 1.33
Disability			
Achilles Tendon Rupture Score[43]	10-item self-reported measure of symptoms and physical activity after treatment of Achilles tendon rupture Each item is scored on 11-point scale (0–10), with a possible total of 100 points, where 0 represents "major limitations/symptoms" and 100 represents "no limitations/symptoms"	ICC = 0.98	MCID = 10
American Orthopedic Foot & Ankle[44-47] Society	Clinical rating system consisting of 4 rating scales corresponding to anatomic region: ankle-hindfoot, midfoot, hallux metatarsophalangeal-interphalangeal, lesser metatarsophalangeal-interphalangeal Assessed using three subscales (function, pain, and alignment), but often utilizes the subjective portions (function and pain) implemented as a patient-reported measure Each scale is scored differently, with the ankle-hindfoot scale measuring pain on a scale of 1–4 and function out of possible 11 points Total score is converted to a percentage, where 0 represents "no symptoms/limitations" and 100 represents "extreme symptoms/limitations"	ICC = 0.75 (ankle-hindfoot)	MCID = 4.7 (ankle-hindfoot)
Foot and Ankle Disability Index[48,49]	Region-specific self-report of function with two components, FADI with 26 items and FADI Sport with 8 items Each item is scored 0–4, totaling 104 for FADI and 32 for FADI Sport Each is separately converted to a percentage, with 100% representing no dysfunction	ICC = 0.89 (FADI), 0.84 (Sport)	MDC = 4.48 (FADI), 6.39 (FADI Sport)
Knee Injury Osteoarthritis Outcome Score[50-52]	42-item self-administered questionnaire for patients with knee injury and osteoarthritis 5 subscales (pain, other symptoms, function in daily living [ADL], function in sport and recreation [Sport/Rec], and knee-related quality of life [QoL]) are scored separately on a 5-point Likert scale from 0–4, with 0 representing "no problems" and 4 representing "extreme problems" Scores are transformed to 100% scale, where 0 represents extreme knee problems and 100 represents no knee problems No aggregate score is calculated	ICC = 0.85 (pain), 0.93 (symptoms), 0.75 (ADL), 0.81 (Sport/Rec), 0.86 (QoL)	MCID = 15.4 (pain), 15.1 (symptoms), 17 (ADL), 11.2 (Sport/Rec), 16.5 (QoL)

Outcome Measure	Description	Reliability	MDC/MCID
Victorian Institute of Sport Assessment Questionnaire[53]	8-item self-reported questionnaires assessing the severity of symptoms in patients with lower extremity tendinopathies Six of the items rate pain during daily activities and functional tasks, while two items inform the impact of tendinopathy on physical activity or sports participation The sum of the scores equals 100 points, where 100 represents "fully functional and asymptomatic" VISA-A: Achilles tendinopathy VISA-P: patellar tendinopathy	ICC (pooled) = 0.92 (VISA-A), 0.96 (VISA-P)	MIC = 6.5 (VISA-A), 16 (VISA-P)
Western Ontario and McMaster Universities Osteoarthritis Index[54,55]	24-item disease-specific self-reported multi-dimensional questionnaire assessing pain, stiffness, and physical functional disability 3 subscales (pain, stiffness, and physical function) are scored separately on a 5-point Likert scale from 0–4, with 0 representing "no problems" and 4 representing "extreme problems" Total score: 20 (pain), 8 (stiffness), 68 (physical function), 0–98 (total)	ICC = 0.86 (pain), 0.68 (stiffness), 0.89 (physical function)	MCID = 4.2 (pain), 1.9 (stiffness), 10.1 (physical function). 16.1 (total)
Quality of Life (QoL)			
EuroQoL-5 Dimension[56-58]	5-item self-reported measure of quality of life assessed across 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) Each dimension is assessed on a scale of 0–100, where 0 represents "worst imaginable health" and 100 represents "best imaginable health" Converted to total score from 0–100	ICC ≥ 0.77	MIC = 0.09
Short Form-36[59-61]	36-item self-reported quality of life tool measured across 8 domains: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to emotional problems, general mental health, social functioning, energy/vitality, and general health perception Each item is scored from 0–100 and averaged to get scale score for each domain out of 100, with higher scores indicating a more favorable health state	ICC = 0.72–0.95 (across domains)	MCID = 10 (physical functioning)

ADL, activities of daily living; CI, confidence interval; FADI, Foot and Ankle Disability Index; ICC, intraclass correlation coefficient; MCID, minimal clinically important difference; MDC, minimal detectable change; MIC, minimally important change; QoL, quality of life; VISA-A, Victorian Institute of Sport Assessment Questionnaire-Achilles Tendon; VISA-P, Victorian Institute of Sport Assessment Questionnaire-Patellar Tendon.

represented small effect, 0.5 represented moderate effect, and 0.8 represented a large effect.[66]

Separate meta-analyses were conducted for each pathology comparing PRP to a comparison or control group for their effect on pain and disability in both short and long terms when data were available. Sensitivity analyses were conducted for disability in Achilles tendinopathy to remove Kearney et al 2013,[31] as it compared PRP alone to exercise alone rather than PRP and exercise compared to placebo and exercise. Where statistical pooling was not possible, findings were presented in narrative form.

Table 4. Risk of Bias Criteria Outlined by the Cochrane Collaboration

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Providers	Blinding of Outcome Assessors	Incomplete Outcome Data – Dropouts	Incomplete Outcome Data – ITT Analysis	Selective Reporting	Group Similarity at Base Line	Influence of Co-interventions	Compliance with Interventions	Timing of Outcome Assessments	Total
Achilles rupture													
Boesen et al. 2020[21]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	11/12
Keene et al. 2019[32]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	11/12
Achilles tendinopathy													
Boesen et al. 2017[22]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	11/12
de Jonge et al. 2011[25]	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	10/12
de Vos et al. 2010[26]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12/12
Kearney et al. 2013[31]	Y	Y	N	N	Y	Y	Y	Y	U	Y	Y	Y	9/12
Krogh et al. 2016[33]	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	8/12
Lateral ankle sprain													
Blanco-Rivera et al. 2019[20]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	11/12
High ankle sprain													
Laver et al. 2014[34]	Y	U	N	Y	U	Y	Y	Y	Y	Y	U	Y	8/12
Hamstring injury													
Hamid et al. 2014[28]	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	10/12
Hamilton et al. 2015[29]	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	10/12
Reurink et al. 2014[36]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12/12
Reurink et al. 2015[37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12/12
Knee osteoarthritis													
Angoorani et al. 2015[19]	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	9/12
Elik et al. 2020[27]	Y	U	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	10/12
Acute muscle injury													
Bubnov et al. 2013[23]	U	U	N	N	U	Y	Y	Y	U	Y	Y	Y	6/12
Rossi et al. 2016[38]	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	10/12
Patellar tendinopathy													
Scott et al. 2019[39]	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y	9/12
Plantar fasciitis													
Chew et al. 2013[24]	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y	Y	9/12
Johnson-Lynn et al. 2018[30]	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	10/12
Mahindra et al. 2016[35]	Y	Y	Y	N	Y	U	Y	Y	Y	Y	Y	Y	10/12

The risk of bias criteria outlined by the Cochrane Collaboration were used and the results were labeled as Yes (Y) = 1; No (N) = 0; Unsure (U) = 0.[62]

Table 5. GRADE Levels of Evidence[62]

Level of Evidence	Description
High quality	Further research is very unlikely to change confidence in estimate of effect.
Moderate quality	Further research is likely to have an important impact on confidence in estimate of effect and may change the estimate.
Low quality	Further research is very likely to have an important impact on confidence in estimate of effect and is likely to change the estimate.
Very low quality	Very little confidence in estimate effect.
No evidence	No RCTs were identified that addressed this outcome.

RESULTS

Study selection

The search identified 485 studies, with an additional 12 identified manually. In all, 41 full-text articles were assessed for eligibility, with 21 articles meeting the inclusion criteria (Figure 1).[19-39]

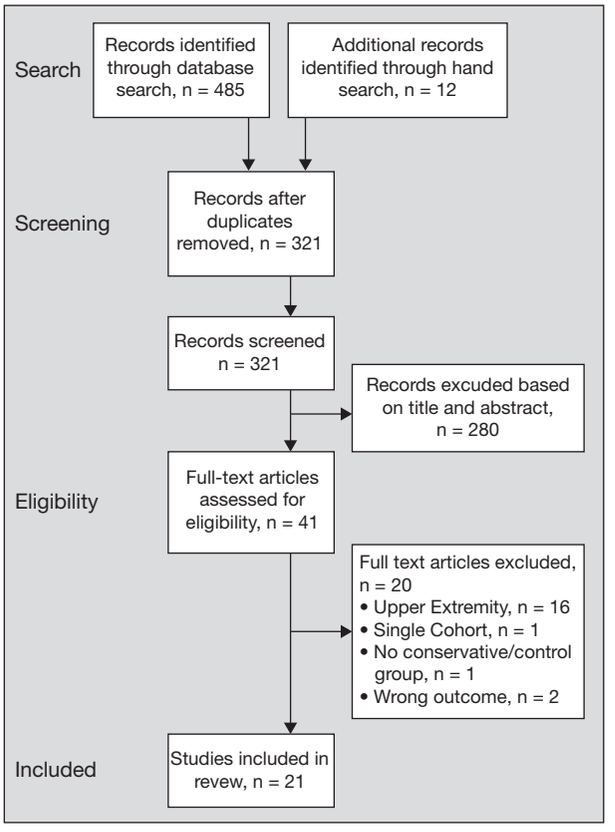

Figure 1. PRISMA flow diagram.

Characteristics of included studies

The average score across studies on the RoB Tool was 9.9 out of 12 (range 6–12; Table 4). The most common sources of bias were blinding of participants, providers, and outcome assessors, leading to potential performance and detection bias.

Across studies, there were a total of 1160 participants, 31% females and 69% males. All studies included patients with various LE musculoskeletal pathologies: Achilles rupture (2),[21,32] Achilles tendinopathy (5),[22,25,26,31,33] lateral ankle sprain (1),[20] high ankle sprain (1),[34] hamstring injury (4),[28,29,36,37] knee osteoarthritis (2),[19,27] acute muscle injury (2),[23,38] patellar tendinopathy (1),[39] and plantar fasciitis (3)[24,30,35] (Table 2). Of the 21 studies, 14 assessed pain[19,20,22-24,27,30-33,35,37-39] (VAS, NPRS, KOOS, and EQ-5D), 13 assessed disability[19-22,24-27,31-33,35,39] (ATRS, AOFAS, FADI, KOOS, VISA-A, VISA-P, and WOMAC), 4 assessed quality of life[19,27,31,32] (EQ-5D, SF-36, and KOOS), 1 assessed strength,[23] 3 assessed the heel rise test[21,22,32] (work, height, and endurance), 1 assessed range of motion,[23] 5 assessed return to play,[28,29,34,36,38] and 4 assessed reinjury rate[28,29,36-38] (Table 6).

Achilles rupture

Two studies[21,32] included 270 participants, 21% females, with an RoB of 11 out of 12. Both studies compared PRP and immobilization and exercise/physical therapy to placebo and immobilization and exercise/physical therapy.

Meta-analyses (n = 270) revealed a nonsignificant effect on disability at both short-term (MD –1.49; 95% CI: –5.15, 2.17; I^2 = 0%; P = 0.42) and long term (MD –0.41; 95% CI: –2.53, 3.35; I^2 = 0%; P = 0.78) follow-up (Figures 2 and 3). One study[32] demonstrated no statistical significance between group differences for pain, and neither study demonstrated significance between group differences in heel rise work,[21] height,[21] and endurance.[32]

Table 6. Results of Included Studies

Study	Outcome	Intervention group[a]		Comparison group[a]		Between group differences (95% CI)	
Achilles rupture							
Boesen et al. 2020[21]	ATRS	Pre	13.0 ± 3.5	Pre	16.5 ± 6.3		
		3 months	52.4 ± 12.07*	3 months	54.0 ± 10.3*	3 months	NS
		6 months	79.8 ± 9.8*	6 months	78.3 ± 10.7*	6 months	NS
		9 months	85.8 ± 8.5*	9 months	83.7 ± 10.3*	9 months	NS
		12 months	90.1 ± 5.4*	12 months	88.8 ± 7.6*	12 months	NS
Keene et al. 2019[32]	VAS	Pre	34 (9–63)[a]	Pre	21.5 (9–54)[d]		
		14 days	9.55 ± 21.45	14 days	13.57 ± 21.51	14 days	NS
	ATRS	Pre	14.09 ± 16.97	Pre	11.668 ± 16.66		
		4 weeks	28.46 ± 16.76	4 weeks	30.61 ± 16.23	4 weeks	NS
		7 weeks	37.58 ± 16.61	7 weeks	38.62 ± 16.42	7 weeks	NS
		13 weeks	51.66 ± 16.79	13 weeks	53.11 ± 16.51	13 weeks	NS
		24 weeks	64.99 ± 16.48	24 weeks	65.53 ± 16.17	24 weeks	NS
Achilles tendinopathy							
Boesen et al. 2017[22]	VAS (mm)	Pre	53.0 ± 21.0	Pre	45.0 ± 23.0		
		6 weeks	37.3 ± 30.0*	6 weeks	22.5 ± 21.9*	6 weeks	*P < 0.05, favoring PRP
		12 weeks	40.9 ± 31.3*	12 weeks	29.5 ± 27.3*	12 weeks	*P < 0.05, favoring PRP
		24 weeks	37.1 ± 27.7*	24 weeks	18.1 ± 26.8*	24 weeks	*P < 0.05, favoring PRP
	VISA-A	Pre	58.1 ± 12.4	Pre	59.2 ± 10.1		
		6 weeks	13.8 ± 18.3*	6 weeks	9.9 ± 14.8*	6 weeks	*P < 0.01, favoring PRP
		12 weeks	14.8 ± 13.9*	12 weeks	10.6 ± 13.4*	12 weeks	*P < 0.01, favoring PRP
		24 weeks	19.6 ± 20.1*	24 weeks	8.8 ± 14.8*	24 weeks	*P < 0.01, favoring PRP
de Jonge et al. 2011[25]	VISA-A	Pre	46.7 ± 17.0	Pre	52.6 ± 8.1		
		1 year	78.2 ± 27.2*	1 year	77.6 ± 18.0*	1 year	NS
de Vos et al. 2010[26]	VISA-A	Pre	46.7 ± 16.2	Pre	52.6 ± 19.0		
		Δ6 weeks	7.8 ± 17.1*	Δ6 weeks	4.6 ± 17.6*	6 weeks	NS
		Δ12 weeks	9.6 ± 20.1*	Δ12 weeks	10.1 ± 20.0*	12 weeks	NS
		Δ24 weeks	21.7 ± 22.1*	Δ24 weeks	20.5 ± 22.5*	24 weeks	NS
Kearney et al. 2013[31]	VISA-A	Pre	41.0 ± 16.0	Pre	36.0 ± 21.0		
		6 weeks	56.0 ± 30.0*	6 weeks	49.0 ± 26.0*	6 weeks	NS
		3 months	63.0 ± 29.0*	3 months	56.0 ± 27.0*	3 months	NS
		6 months	76.0 ± 23.0*	6 months	57.0 ± 27.0*	6 months	NS
	EQ-5D	Pre	0.75 ± 0.14	Pre	0.56 ± 0.32		
		6 weeks	0.73 ± 0.16	6 weeks	0.67 ± 0.38	6 weeks	NS
		3 months	0.74 ± 0.28	3 months	0.66 ± 0.41	3 months	NS
		6 months	0.82 ± 0.35	6 months	0.74 ± 0.39	6 months	NS
	EQ-5D VAS	Pre	61.0 ± 23.0	Pre	67.0 ± 21.0		
		6 weeks	68.0 ± 23.0	6 weeks	71.0 ± 20.0	6 weeks	NS
		3 months	69.0 ± 32.0	3 months	68.0 ± 29.0	3 months	NS
		6 months	68.0 ± 30.0	6 months	76.0 ± 20.0	6 months	NS
Krogh et al. 2016[33]	NPRS[c]	Pre	3.1 ± 2.5	Pre	4.0 ± 3.0		
		Δ3 months	0.2 ± 2.4	Δ3 months	-1.4 ± 2.4	3 months	NS
	VISA-A	Pre	31.7 ± 20.7	Pre	37.1 ± 16.0		
		Δ3 months	3.4 ± 21.8	Δ3 months	4.8 ± 17.0	Δ3 months	NS
		Δ6 months[c]	2.6 ± 19.4	Δ6 months[c]	10.1 ± 20.8	Δ 6 months	NS
		Δ12 months[c]	0.5 ± 15.9	Δ12 months[c]	14.6 ± 30.5	Δ12 months	NS

(*Continuous*)

Table 6. (Continued)

Study	Outcome	Intervention group[a]		Comparison group[a]		Between group differences (95% CI)	
Lateral ankle sprain							
Blanco-Rivera et al. 2019[20]	VAS (cm)	Pre	7.5 ± 1.9	Pre	8.0 ± 1.2		
		3 weeks	3.0 ± 0.8	3 weeks	5.8 ± 0.6	3 weeks	*P < 0.0001, favoring PRP
		5 weeks	2.3 ± 0.5	5 weeks	4.0 ± 0.5	5 weeks	*P < 0.0001, favoring PRP
		8 weeks	0.3 ± 0.5	8 weeks	1.4 ± 0.5	8 weeks	*P < 0.0001, favoring PRP
		24 weeks	0.1 ± 0.3	24 weeks	0.2 ± 0.4	24 weeks	NS
	AOFAS	Pre		Pre			
		3 weeks	86.5 ± 3.0	3 weeks	82.1 ± 3.7	3 weeks	*P = 0.007, favoring PRP
		5 weeks	89.5 ± 1.8	5 weeks	87.7 ± 1.5	5 weeks	*P = 0.026, favoring PRP
		8 weeks	98.2 ± 4.0	8 weeks	89.8 ± 0.6	8 weeks	*P < 0.0001, favoring PRP
		24 weeks	98.5 ± 3.4	24 weeks	97.8 ± 2.6	24 weeks	NS
	FADI	Pre		Pre			
		3 weeks	122.0 ± 8.8	3 weeks	117.1 ± 14.4	3 weeks	NS
		5 weeks	127.2 ± 8.7	5 weeks	124.6 ± 8.7	5 weeks	NS
		8 weeks	133.1 ± 1.0	8 weeks	129.5 ± 4.0	8 weeks	*P = 0.0003, favoring PRP
		24 weeks	135.4 ± 1.0	24 weeks	135.3 ± 1.0	24 weeks	NS
High ankle sprain							
Laver et al. 2014[34]	RTP (days)		40.8 ± 8.9		59.6 ± 12.0		*P = 0.006, favoring PRP
Hamstring injury							
Hamid et al. 2014[28]	RTP (days)		26.7 ± 5		42.5 ± 20.6		*P = 0.017, favoring PRP
Hamilton et al. 2015[29]	RTP (days) Median (95% CI)		21 (17.9, 24.1)		25 (21.5, 28.5)		NS
	Reinjury rate (participant)	2 months	2 (8%)	2 months	2 (7.7%)	2 months	NS
		6 months	2 (7.7%)	6 months	3 (10.3%)	6 months	NS
Reurink et al. 2014[36]	RTP (days) Median (IQR)	6-month F/U	42 (30–58)	6-month F/U	42 (37–56)		NS
	Reinjury rate (participant)	6-month F/U	7 (16%)	6-month F/U	5 (14%)		NS
Reurink et al. 2015[37]	NPRS	Pre	NA	Pre	NA		
		1 week	0.7 ± 1.5	1 week	0.5 ± 1.2	1 week	NS
		4 weeks	0.2 ± 0.8	4 weeks	0.2 ± 0.8	4 weeks	NS
		10 weeks	0.1 ± 0.4	10 weeks	0.2 ± 0.7	10 weeks	NS
	Reinjury rate (participant)	1-year F/U	10 (27%)	1-year F/U	11 (30%)		NS
Knee osteoarthritis							
Angoorani et al. 2015[19]	VAS	Pre	NA	Pre	NA		
		4 weeks	*	4 weeks	*	4 weeks	NS
		8 weeks	*	8 weeks	*	8 weeks	NS
	KOOS Pain	Pre	44.9 ± 3.43	Pre	41.3 ± 3.43		
		4 weeks	54.4 ± 4.15*	4 weeks	46.7 ± 3.14*	4 weeks	NS
		8 weeks	50.7 ± 3.24	8 weeks	44.2 ± 3.88	8 weeks	NS

Study	Outcome	Intervention group[a]		Comparison group[a]		Between group differences (95% CI)	
	KOOS Symptoms	Pre	51.5 ± 4.47	Pre	50.3 ± 3.87		
		4 weeks	63.6 ± 4.23*	4 weeks	51.7 ± 3.56	4 weeks	*P = 0.01, favoring PRP
		8 weeks	61.5 ± 3.86	8 weeks	52.0 ± 3.96	8 weeks	NS
	KOOS ADL	Pre	48.3 ± 3.81	Pre	42.4 ± 4.09		
		4 weeks	58.7 ± 4.08*	4 weeks	46.9 ± 3.68	4 weeks	NS
		8 weeks	54.4 ± 3.35*	8 weeks	44.2 ± 4.36	8 weeks	NS
	KOOS Sport/Rec	Pre	23.8 ± 4.87	Pre	28.4 ± 6.16		
		4 weeks	22.9 ± 4.68	4 weeks	27.6 ± 6.11	4 weeks	NS
		8 weeks	21.3 ± 4.33	8 weeks	25.4 ± 5.31	8 weeks	NS
	KOOS QOL	Pre	17.1 ± 2.62	Pre	20.6 ± 3.65		
		4 weeks	23.0 ± 3.14	4 weeks	18.4 ± .68	4 weeks	NS
		8 weeks	22.6 ± 2.49	8 weeks	17.6 ± 2.58	8 weeks	NS
Elik et al. 2020[27]	VAS	Pre	3.87 ± 2.14	Pre	4.93 ± 1.68		
		1 month	1.80 ± 1.67*	1 month	3.67 ± 1.86*	1 month	*P < 0.001, favoring PRP
		6 months	1.20 ± 1.56*	6 months	3.37 ± 2.32*	6 months	*P < 0.001, favoring PRP
	WOMAC	Pre	56.40 ± 18.71	Pre	57.04 ± 15.12		
		1 month	35.77 ± 17.57*	1 month	43.93 ± 17.99*	1 month	NS
		6 months	24.87 ± 18.79*	6 months	42.37 ± 18.64*	6 months	*P < 0.05, favoring PRP
Acute muscle injury							
Bubnov et al. 2013[23]	VAS	Pre	NA	Pre	NA		
		7 days	NA	7 days	NA	7 days	*Favoring PRP
		14 days	NA	14 days	NA	14 days	*Favoring PRP
		21 days	NA	21 days	NA	21 days	*Favoring PRP
		28 days	NA	28 days	NA	28 days	NS
	ROM	Pre	NA	Pre	NA		
		7 days	NA	7 days	NA	7 days	*Favoring PRP
		14 days	NA	14 days	NA	14 days	*Favoring PRP
		21 days	NA	21 days	NA	21 days	*Favoring PRP
		28 days	NA	28 days	NA	28 days	*Favoring PRP
	Strength	Pre	NA	Pre	NA		
		7 days	NA	7 days	NA	7 days	*Favoring PRP
		14 days	NA	14 days	NA	14 days	*Favoring PRP
		21 days	NA	21 days	NA	21 days	*Favoring PRP
		28 days	NA	28 days	NA	28 days	NS
Rossi et al. 2016[38]	VAS	Pre	4.7 ± 1.2	Pre	4.8 ± 0.9		
		2 months	NA	2 months	NA	2 months	*P = 0.023, Favoring PRP
		12 months	NA	12 months	NA	12 months	*P = 0.023, Favoring PRP
		24 months	NA	24 months	NA	24 months	*P = 0.023, Favoring PRP
	RTP (days)		21.2 ± 3.1		25.0 ± 2.8		*P = 0.001, Favoring PRP
	Reinjury rate (participant)		2 (5.7%)		4 (10%)		NS
Patellar tendinopathy							
Scott et al. 2019[39]	NPRS	Pre	4.4 ± 2.0	Pre	5.0 ± 2.0		
		6 weeks	3.6 ± 2.0	6 weeks	3.4 ± 2.2	6 weeks	NS
		12 weeks	3.4 ± 1.9	12 weeks	2.9 ± 2.1	12 weeks	NS
		24 weeks	3.3 ± 1.5	24 weeks	3.1 ± 2.1	24 weeks	NS
		52 weeks	4.0 ± 2.4	52 weeks	2.0 ± 1.9	52 weeks	NS

(*Continuous*)

Table 6. (Continued)

Study	Outcome	Intervention group[a]		Comparison group[a]		Between group differences (95% CI)	
	VISA-P	Pre	49 ± 16	Pre	49 ± 14		
		6 weeks	55 ± 22	6 weeks	63 ± 19	6 weeks	NS
		12 weeks	63 ± 22	12 weeks	69 ± 18	12 weeks	NS
		24 weeks	58 ± 22	24 weeks	74 ± 18	24 weeks	NS
		52 weeks	58 ± 29	52 weeks	80 ± 18	52 weeks	NS
Plantar fasciitis							
Chew et al. 2013[24]	VAS Median (range)	Pre	7 (4–10)	Pre	6 (3–8)		
		1 month	4 (1–10)	1 month	5 (3–8)	1 month	*P = 0.036, favoring ACP
		3 months	4 (0–8)	3 months	4 (1–9)	3 months	NS
		6 months	2 (0–6)	6 months	3 (0–7)	6 months	NS
	AOFAS	Pre	65 (38–77)	Pre	72 (51–77)		
		1 month	75 (35–84)	1 month	75 (55–82)	1 month	NS
		3 months	86 (67–100)	3 months	80 (53–90)	3 months	*P = 0.004, favoring ACP
		6 months	90 (77–100)	6 months	87 (73–100)	6 months	*P = 0.013, favoring ACP
Johnson-Lynn et al. 2018[30]	VAS	Pre	68.29 ± 25.28	Pre	77.43 ± 22.16		
		6 months	31.11 ± 26.90*	6 months	35.18 ± 30.46*	6 months	NS
		12 months	23.71 ± 23.68*	12 months	36.50 ± 31.92*	12 months	NS
Mahindra et al. 2016[35]	VAS	Pre	7.44 ± 1.04	Pre	7.56 ± 1.15		
		3 weeks	3.76 ± 1.53*	3 weeks	7.12 ± 1.12	3 weeks	*Favoring PRP
		3 months	2.52 ± 1.71*	3 months	7.44 ± 1.04	3 months	*Favoring PRP
	AOFAS	Pre	51.56 ± 11.10	Pre	50.28 ± 11.01		
		3 weeks	83.92 ± 12.12*	3 weeks	53.88 ± 11.81	3 weeks	*Favoring PRP
		3 months	88.24 ± 8.76*	3 months	50.84 ± 10.76	3 months	*Favoring PRP

ATRS, Achilles tendon Total Rupture Score; AOFAS, American Orthopaedic Foot & Ankle Society; ACP, autologous conditioned plasma; CI, confidence interval; EQ-5D, EuroQoL-5 Dimension; F/U, follow-up; FADI, Foot and Ankle Disability Index; IQR, interquartile range; KOOS, Knee Injury Osteoarthritis Outcome Score; NS, not significant; NPRS, Numeric Pain Rating Scale; ROM, range of motion; RTP, return to play; VISA-A, Victorian Institute of Sport Assessment Questionnaire-Achilles Tendon; VISA-P, Victorian Institute of Sport Assessment Questionnaire-Patellar Tendon; VAS, Visual Analog Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a]*Data are presented as mean ± standard deviation (SD), unless indicated otherwise. In the event that standard error (SE) was reported, standard deviation was calculated using the following formula: SD = SE*√(n). In the event that CI was reported, standard deviation was calculated using the following formula: SD = √(n)*(upper bound-lower bound)/3.92.*

[b]*Only median and IQR reported for pre-treatment assessment.*

[c]*Positive values for change scores indicate improvement, whereas negative values indicate worsening.*

[d]*Data used were last observation carried forward.*

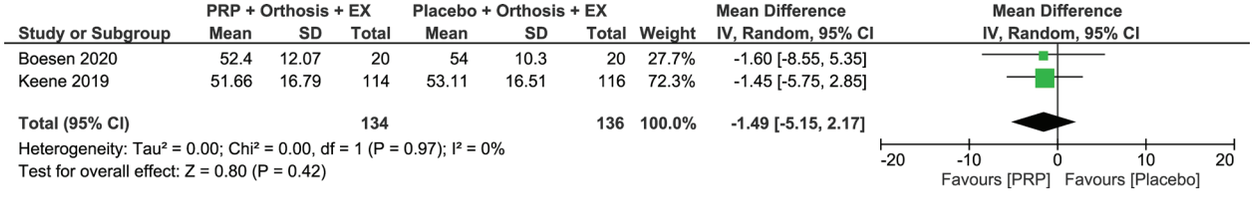

Figure 2. Meta-analysis of PRP and immobilization and exercise/physical therapy versus placebo and immobilization and exercise/physical therapy in Achilles rupture for disability in the short term (3 months).

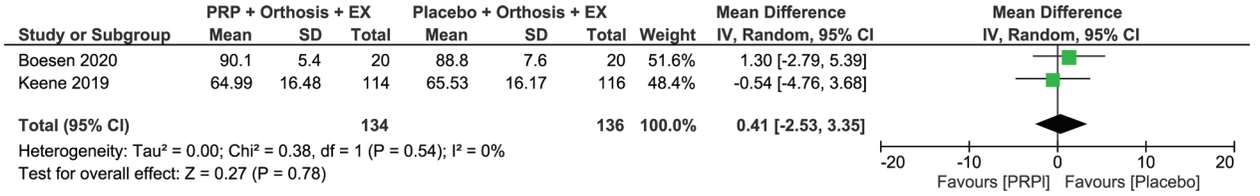

Figure 3. Meta-analysis of PRP and immobilization and exercise/physical therapy versus placebo and immobilization and exercise/physical therapy in Achilles rupture for disability in the long term (12 months).

Achilles tendinopathy

Five studies[22,25,26,31,33] included 212 participants, with 33% females. The average RoB score was 10 out of 12 (range 8–12). Four studies[22,25,26,33] compared PRP and exercise to placebo and exercise, while one study[31] compared PRP alone to exercise alone.

Meta-analyses of two studies[22,33] (n = 64) revealed a nonsignificant effect on pain (SMD –0.09; 95% CI: –1.10, 0.91; I^2 = 73%; P = 0.85) at short-term follow-up (Figure 4). Meta-analyses of four studies[22,26,31,33] (n = 138) revealed a nonsignificant effect on disability (SMD 0.10; 95% CI: –0.23, 0.43; I^2 = 0%; P = 0.56) at short-term follow-up (Figure 5). Meta-analyses of five studies[22,25,26,31,33] (n = 192) revealed a nonsignificant effect on disability (SMD 0.16; 95% CI: –0.23, 0.54; I^2 = 40%; P = 0.42) at long-term follow-up (Figure 6). Sensitivity analysis removing Kearney et al 2013[31] demonstrated similar non-significant effects in both the short and long term. One study demonstrated no statistical significance between group differences in the heel rise test,[22] with another study with similar results for quality of life.[31]

Lateral ankle sprain

Study conducted by Blanco-Rivera et al.[20] included 23 participants, 43% females, with an RoB score of 11 out of 12, comparing PRP, immobilization, and rehabilitation to immobilization and rehabilitation.

Blanco-Rivera et al.[20] demonstrated statistical significance between group differences on pain and disability on AOFAS, favoring PRP, immobilization, and rehabilitation in the short term but not for the long-term follow-up. Statistical significance

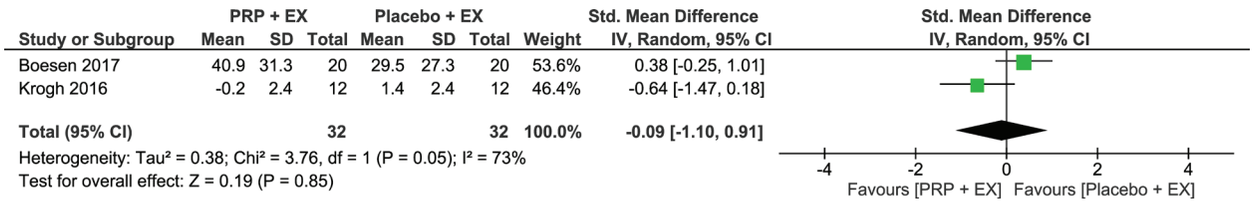

Figure 4. Meta-analysis of PRP and exercise versus placebo and exercise in Achilles tendinopathy for pain in the short term (3 months).

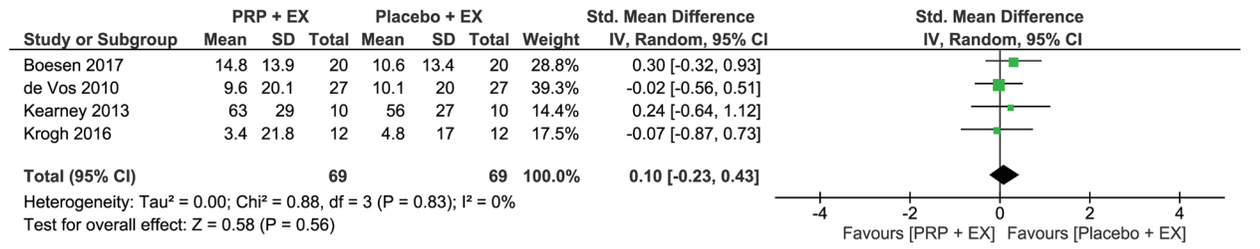

Figure 5. Meta-analysis of PRP and exercise versus placebo and exercise in Achilles tendinopathy for disability in the short term (3 months).

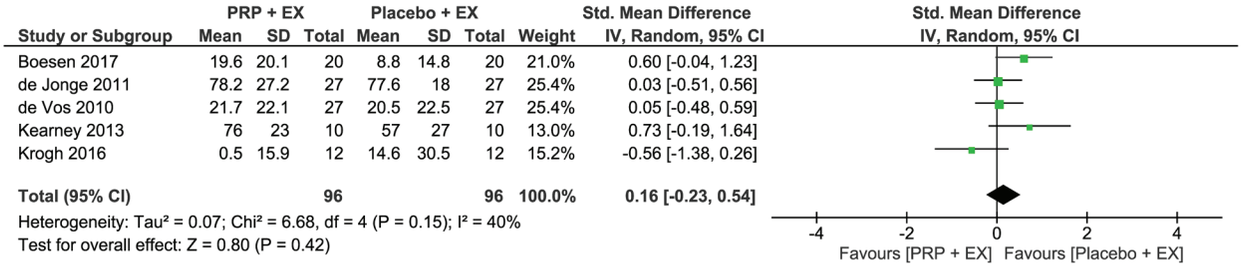

Figure 6. Meta-analysis of PRP and exercise versus placebo and exercise in Achilles tendinopathy for disability in the long term (12 months).

between group differences was found for disability on FADI at 8-week follow-up only.

High ankle sprain

Study conducted by Laver et al.[34] included 16 participants, with an RoB score of 8 out of 12, comparing PRP, immobilization, and physical therapy to immobilization and physical therapy. Statistical significance between group differences in return to play was demonstrated, with the PRP group returning earlier at an average of 40.8 days versus 59.6 days in the comparison group.

Hamstring injury

Four studies[28,29,36,37] included 198 participants, with 4% females. The average RoB score was 11 out of 12 (range 10–12). Studies conducted by Hamid et al.[28,29] compared PRP and physical therapy to physical therapy alone, while study conducted by Reurink et al. (2014)[36] compared PRP and physical therapy to placebo and physical therapy, with Reurink et al. (2015) as a follow-up study[37] with long-term data. No statistically significant differences were discovered for return to play,[29,36] reinjury rate,[29,36,37] or pain,[37] except for Hamid et al. 2014,[28] which demonstrated an earlier return to play in the PRP group with an average of 26.6 days versus 42.5 days in the comparison group.

Knee osteoarthritis

Studies conducted by Angoorani et al.[19,27] included 114 participants, with 90% females. The average RoB score was 9.5 out of 12 (range 9–10). Angoorani et al.[19] compared PRP to transcutaneous electrical stimulation and exercise, while Elik et al.[27] compared PRP and exercise to placebo and exercise.

Study conducted by Elik et al.[27] demonstrated statistical significance between group differences on pain and SF-36 physical function subscale in both short and long terms, and disability and SF-36 mental health subscale in the long term, favoring PRP and exercise, while the study conducted by Angoorani et al.[19] only demonstrated statistical significance between group differences in KOOS symptom score at 4 weeks, favoring PRP. No statistical significance between group differences was found for pain or any other KOOS subscale.[19]

Acute muscle injury

Studies conducted by Bubnov et al.[23,38] included 109 participants, with 16% females. The average RoB score was 8 out of 12 (range 6–10). Study conducted by Bubnov et al.[23] compared PRP and conventional conservative therapy to conventional conservative therapy alone, while the other conducted by Rossi et al.[38] compared PRP and physical therapy to physical therapy alone. Bubnov et al.[23] included participants with thigh trauma (53%), foot and ankle trauma (29%), and shoulder trauma (18%). Rossi et al.[38] included participants with hamstring injury (34%), quadriceps injury (15%), and gastrocnemius injury (23%). Both studies demonstrated statistical significance between group differences in pain favoring PRP, while Bubnov et al.[23] found statistical significance between group differences for ROM and strength during short-term follow-up. Rossi et al.[38] demonstrated statistical significance between group differences in return to

play, with the PRP and physical therapy group demonstrating an earlier return (21.2 days) compared to physical therapy alone (25 days), but no significance between group differences in reinjury rate.

Patellar tendinopathy

Study conducted by Scott et al.[39] included 61 participants, with 12% female, with an average RoB score of 9 out of 12, comparing PRP and physical therapy to placebo and physical therapy. The results demonstrated no statistical significance between group differences on pain or disability.

Plantar fasciitis

Three studies[24,30,35] included 157 participants, with 58% females. The average RoB score was 9.7 (range 9–10). Study conducted by Johnson-Lynn et al.[30] compared PRP, immobilization, and physical therapy to placebo, immobilization, and physical therapy, while another[35] compared PRP and physical therapy to placebo and physical therapy. The third study[24] compared autologous conditioned plasma (ACP) and conventional treatment to conventional treatment alone.

Two studies demonstrated statistical significance between group differences on pain in the short term[24,35] and disability in both short[24,35] and long[24] terms, one favoring ACP and conventional treatment and the other favoring PRP and physical therapy. Johnson-Lynn et al.[30] found no statistically significant difference between group differences on pain.

DISCUSSION

This systematic review included 21 studies on various LE musculoskeletal pathologies, with data only permitting meta-analyses on Achilles tendon rupture[21,32] and Achilles tendinopathy.[22,25,26,31,33] All meta-analyses revealed nonsignificant effects for pain in the short term, and disability at both short- and long-term follow-up when comparing PRP + immobilization and exercise (high level of evidence) to placebo + immobilization and exercise for the management of Achilles tendon rupture, and when comparing PRP + exercise (very low to low level of evidence) to placebo + exercise for the management of Achilles tendinopathy (Table 7). It is important to note that the high level of evidence for nonsignificant findings suggests that the addition of PRP to exercise is not clinically warranted for Achilles tendon rupture. However, it is unclear whether the addition of PRP would benefit patients with Achilles tendinopathy, given the very low to low level of evidence. Clinically, it would be more logical that the addition of PRP would yield positive results in the presence of tendinopathy because of its potential tissue-healing effects, questioning the overall confidence in the findings.

While all meta-analyses demonstrated nonsignificant effects, some individual studies established significant difference between group differences. Individual studies have demonstrated the effectiveness of the addition of PRP to exercise on pain in various pathologies, including lateral ankle sprain in the short term,[20] knee OA in both short and long terms,[27] acute muscle injury,[23,38] and plantar fasciitis in the short term,[24,35] while it had no effect on hamstring injury[37] or patellar tendinopathy.[39] Additionally, PRP in conjunction with exercise demonstrated a positive effect on disability in studies including patients with lateral ankle sprains,[20] knee OA,[27] and plantar fasciitis,[24,35] but not in patients with patellar tendinopathy.[39] Across the spectrum of LE musculoskeletal pathologies, three studies[28,34,38] demonstrated an earlier return to play in the group that received PRP (high ankle sprain, hamstring injury, and acute muscle injury); however, no differences in reinjury rate were observed in two studies[29,36] looking at hamstring injury.[29,36-38]

Despite the fact that most of the articles included in this review addressed patients with muscular, tendinous, or ligamentous pathology, the results across studies were surprisingly inconsistent, given the purported physiologic benefits of PRP on soft tissue healing. In order to assess the isolated physiologic changes associated with PRP compared to exercise, study designs must also include a true control group that does not receive any interventions. To this point, it would have been beneficial to address the isolated role of PRP in select LE musculoskeletal pathologies. However, the majority of included studies did not compare PRP and exercise to PRP alone, or PRP alone to exercise alone. Hence, it was difficult to draw firm conclusions on the isolated benefit of PRP, as results were only based on two individual studies within this systematic review.

Table 7. GRADE Evidence Profile

Outcome (n = studies)	Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Level of Evidence
Achilles rupture; 3 months							
Disability [ATRS] (n = 2)	270	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High
Achilles rupture; 12 months							
Disability [ATRS] (n = 2)	270	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High
Achilles tendinopathy; 3 months							
Pain [VAS/NPRS] (n = 2)	64	Serious[a]	Serious[a,i]	Not serious	Serious[c]	None	⊕OOO Very low
Disability [VISA-A] (n = 3)	118	Serious[a]	Not serious	Not serious	Serious[c]	None	⊕⊕OO Low
Achilles tendinopathy; 12 months							
Disability [VISA-A] (n = 4)	172	Serious[a]	Not serious	Not serious	Serious[c]	None	⊕⊕OO Low

ATRS, Achilles tendon Total Rupture Score; NPRS, Numeric Pain Rating Scale; VAS, Visual Analog Scale; VISA-A, Victorian Institute of Sport Assessment Questionnaire-Achilles Tendon.

[a]*Risk of bias associated with performance, detection, attrition, and reporting bias.*

[b]*Studies demonstrate heterogeneity $I^2 > 50\%$.*

[c]*Studies contain small sample sizes.*

To date, this systematic review is the first to address the effectiveness of PRP combined with physical therapy, rehabilitation, or exercise. The strengths of this review included the detailed search strategy, including clinicaltrials.gov, using the Cochrane RoB tool for methodological quality, and performing a GRADE analysis. While there were many strengths of this systemic review, it was not without limitations. A major limitation was the heterogeneity across trials precluding further meta-analysis, particularly those that demonstrated significant findings preventing the ability to provide strong clinical recommendations. Additionally, the focus of this review was not about cost-effectiveness, therefore in the absence of strong positive findings, it was difficult to suggest that clinicians recommend PRP as an adjunct to physical therapy or exercise, as the out of pocket expense to the patient could not be justified. Furthermore, it was plausible that inconsistent findings for the effectiveness of PRP could be related to the absence of standardized protocols for injection dosage and technique. The future studies must strongly consider rigorous and standardized study designs with larger sample sizes for the application of PRP in conjunction with physical exercise.

CONCLUSION

While a number of individual studies demonstrated significant findings across outcomes, the nonsignificant pooled results and inability to perform further meta-analyses made it difficult to provide definitive recommendations for the addition of PRP to physical exercise for LE musculoskeletal pathologies. Future studies should standardized PRP exercise rehabilitation protocols with better dosage parameters, consider larger sample sizes, and have short and long term follow-up periods consistent with the Cochrane Collaboration.

AUTHOR CONTRIBUTIONS

Both authors contributed equally in conception and design, administrative support, provision of study material, collection and assembly of data, data

analysis and interpretation, manuscript writing, and final approval of the manuscript.

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APPENDIX

Section/ Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7 Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7 Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	34
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	26, 31, 34 Tables 2-3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	31, Table 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	34-35
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	34-35
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	31, Table 4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	35

Section/ Topic	#	Checklist Item	Reported on Page #
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	35, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	35-36, Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	44-47, Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	44-48 Table 6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	44, Figures 2-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	35, Table 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	44
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	48-51, Table 7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	51
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	48-51
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	52