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Review Article

Treating hand and foot osteoarthritis using a patient's own blood: A systematic review and meta-analysis of platelet-rich plasma

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ABSTRACT

Background: This study summarizes all literature investigating platelet-rich plasma (PRP) in the treatment of osteoarthritis of the hands and feet.
Materials & methods: This is a PRISMA compliant systematic review of 7 databases and includes a meta-analysis of randomized controlled trial (RCT) data on pain and function.
Results: Nine articles were included in the review. Meta-analysis of 4 RCTs shows PRP significantly improves pain and function versus control. More results are significant at longer duration follow-up.
Conclusions: PRP improves pain and function of osteoarthritis. Heterogeneity and risk-of-bias limit current data, requiring more RCTs to determine any regenerative potential of PRP.
Prospero Systematic Review Registration Number: 136582.

1. Introduction

Osteoarthritis is the most common form of degenerative joint disease and the leading cause of disability in elderly populations. In 2012, approximately 52.5 million (22.7%) adults in the United States carried a diagnosis of osteoarthritis. As the elderly population grows, this incidence is expected to increase.[1–3] In addition to the health implications, osteoarthritis is the second most costly condition in the nation, with medical expenditures reaching an excess of $16.5 billion yearly.[1–4] Healthcare costs and high incidence make this degenerative condition one of the most important chronic conditions in the world.

Osteoarthritis is the breakdown of joint cartilage and its underlying bone resulting in pain, stiffness, and a loss of joint function. Some joints experience osteoarthritis as a normal process of aging,[5] while other joints such as the ankle predominately experience osteoarthritis secondary to trauma that exposes subchondral bone.[6] The size of the osteochondral lesion not only correlates to pain, but predisposes to osteoarthritis.[7]

On a molecular level, hyaline cartilage erosion and an imbalance of pro- and anti-inflammatory cytokines, such as interleukin-1β (IL-1β) and matrix metalloproteinases (MMPs), cause synovitis. Repetitive mechanical stress results in the remodeling of subarticular bone, osteophyte formation, and capsular swelling which leads to the clinical sequelae of osteoarthritis with both the incidence and severity being affected by risk factors including genetics, traumatic injury, and obesity.[8–12] As the disease progresses, the erosion of hyaline cartilage within the joint heals poorly due to minimal intrinsic circulation and ability for regrowth or regeneration.

There are no curative medications, however, in 2019 an exciting discovery was made that the potential for regrowth or regeneration of cartilage is the greatest in the most distal cartilage, such as of the hands and feet.[13] Currently, physicians and patients pursue symptomatic management including thermal modalities, topical capsaicin, non-steroidal anti-inflammatory drugs, and steroid injections.[14] Arthroplasty (e.g. hip replacement) is profoundly effective for large joint osteoarthritis,[15–17] but surgical interventions for small joint hand and foot osteoarthritis remain meager and come at the expense of functionality (e.g. joint fusion, denervation).[18,19] Therefore, interest of patients and providers in intra-articular injection of autologous growth factors, platelet-rich plasma (PRP) in particular, is an exciting option that treats pain, and also carries a possibility for enhancing chondrocyte activity that is the most pronounced in the small joints of the hand and foot.[20–22] While PRP treatments have been reviewed in the context of knee and large joint osteoarthritis,[21–23] no such review has been

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performed on small, distal joint osteoarthritis.

1.1. PRP preparation and mechanism

PRP is an autologous product of whole blood centrifugation which separates blood by density into cellular layers and a supernatant layer. The supernatant is further divided, often by pipetting or by a second centrifugation step, into a platelet-rich segment called platelet-rich plasma (PRP) and a platelet-poor segment termed platelet-poor plasma (PPP). PRP contains a platelet concentration 2–5 times higher than that of normal blood. Many protocols for preparing PRP exist. One researched variant is whether to include the leukocyte-containing buffy coat; the inclusion of this layer provides the designation leukocyte-rich (LR) PRP while the absence of leukocytes is termed leukocyte-poor (LP) PRP.[24] LP-PRP is the standard preparation for osteoarthritis due to in-vitro and animal studies demonstrating that LR PRP induces more IL-1β and less chondrocyte proliferation than LP PRP.[25–28] Furthermore, Intravia et al. tested LR versus LP PRP and both significantly inhibited bacterial growth when compared to normal blood culture, and had no significant difference between each other.[29]

The biomolecular mechanisms by which PRP functions is a topic heavily under study. The current understanding is that local stimuli induce platelet release of a subset of their cytokine and growth factor containing α-granules. In the instance of osteoarthritis, these molecules act predominately via anti-inflammatory cascades to reduce the pain of osteoarthritis.[23,30] The anti-inflammatory effect of PRP includes suppressing the actions of the inflammatory and catabolic cytokines tumor necrosis factor α (TNF-α) and interferon-γ in endothelial cells.[31] Surprisingly, PRP also induces molecules associated with sterile inflammation, such as interleukin-1β (IL-1β), for which the net effect on osteoarthritis chondrocytes is a production of molecules that would ordinarily not be produced in the presence of IL-1β, such as the regenerative building blocks type II collagen and aggrecan, while still resulting in increased production of the chondroprotective hyaluronan by synoviocyte in response to IL-1β.[32–34] Another growth factor, transforming growth factor β1 (TGF-β1), has an antagonistic effect to IL-1β while also increasing differentiation of mesenchymal stem cells into chondrocytes.[35,36] PRP is thought to protect cartilage largely due to IGF-1 and TGF-β1, which promote cell survival and deposition of extracellular matrix.[37] Vascular endothelial growth factor (VEGF) is an important influencer of angiogenesis that is found in PRP, however, its antagonist, thrombospondin (TSP1), is interestingly found in the highest physiologic concentration in platelet α-granules. The net effect of these pro- and anti-angiogenesis proteins may correct the pathologic angiogenesis found in osteoarthritis.[37–40]

These findings promote that PRP may mediate cartilage regeneration in addition to reducing pain. Therefore, this systematic review and meta-analysis aims to summarize all literature on PRP applied for the treatment of small, distal joint osteoarthritis of the hands and feet in order to investigate the therapeutic efficacy and regenerative potential of PRP.

2. Methods

This study was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with the protocol ID 136582 being established prior to the conduct of the review.[41]

2.1. Search strategy

Independent literature searches were performed by two authors (M.I. and J.M.) of all published articles up to June 2019 utilizing: Cochrane Library, Ovid Medline, Ovid Embase, Web of Science, clinicaltrials.gov, World Health Organization Clinical Trials Registry, and EBSCO. The search was conducted in June of 2019 using the search terms: "platelet-rich plasma" OR "platelet rich fibrin" OR "platelet-rich fibrin" OR "platelet gel" OR "autologous conditioned plasma" OR "pure platelet-rich-plasma" OR "platelets" OR platelet concentrate" OR "prp" OR "prgf" OR "acp" AND "arthritis" OR "osteoarthritis" OR "OA." The search strategy was designed and altered as necessary and appropriate to the different databases (Appendix). Bibliographies of included studies were also searched. An additional reviewer (A.E.) assisted in the discussion of study selection in any instance of disagreement between the two reviewers. To capture all published clinical trials, both randomized controlled trials (RCTs) and non-randomized studies of interventions (NRSI) were included. The largest cohort was included in the study if multiple publications described the same cohort. Data extraction was performed by one reviewer (M.I.) using a piloted form excel spreadsheet method, with a second reviewer (A.E.) checking over 90% of the extracted data. Experts in the field of plastic & reconstructive surgery and in the application of PRP were consulted and included in the study.

2.2. Inclusion and exclusion criteria

Included studies: 1) treated patients over the age of 18, 2) used intra-articular injections of PRP, 3) treated osteoarthritis and osteochondral lesions affecting a joint of the hand and foot, 4) had a minimum follow-up of at least 3 months, 5) were published in English.

Excluded studies: 1) were duplicates of studies or cohorts, 2) treated conditions different than osteoarthritis or osteochondral lesions, e.g. (rheumatoid arthritis, epicondylitis, carpal tunnel, plantar fasciitis), 3) treated joints other than the hand, wrist, foot, or ankle, e.g. (knee osteoarthritis, hip osteoarthritis), 4) pending trials, 5) studies with absent baseline functional/pain data, 6) animal studies, case reports, review articles, or retrospective studies, 7) non peer-reviewed "grey" literature.

2.3. Risk of bias

Risk of Bias assessment was performed at a study and outcome level through use of the Cochrane risk-of-bias tool for randomized controlled trials. Study sources of funding and reported conflicts of interest were recorded.

2.4. Outcomes

The primary outcome compared between studies was an assessment of the efficacy of PRP in treating pain using a visual analog scale (VAS) for pain.[26,42–49] Secondary outcomes included adverse reactions, radiographic imaging of the joint space, patient satisfaction,[42,48,49] and measures of joint function using: Foot and Ankle Disability Index,[42] Japanese Society for Surgery of the Foot (JSSF) ankle/hindfoot scale, the Self-Administered Foot Evaluation Questionnaire (SAFE-Q),[43] American Orthopaedic Foot & Ankle Society scale (AOFAS),[44,45] Visual Analog Scale (VAS) for function,[49] Mayo Wrist Score,[26] Disabilities of the Arm, and Shoulder and Hand (DASH).[26,47]

2.5. Statistical data analysis and synthesis

RevMan 5.3.5 (Cochrane Collaboration) software package was utilized for all statistical analysis in this study. Only RCTs were included in the meta-analysis. Dichotomous variables were presented as odds ratios with a 95% CI. To incorporate the heterogeneity between studies, the authors calculated I^2 and $I^2 > 50\%$ was considered to be high heterogeneity and warranted investigation of study details contributing to heterogeneity. Random-effects model was chosen. Data on pain and function were grouped as either short-term, defined as patient follow-up visits taking place less than 6 months after final treatment, and long-term, defined as patient follow-up visits taking place at 6 months or more after final treatment. In the instance that no significant difference was found between treatment and control, an analysis was performed

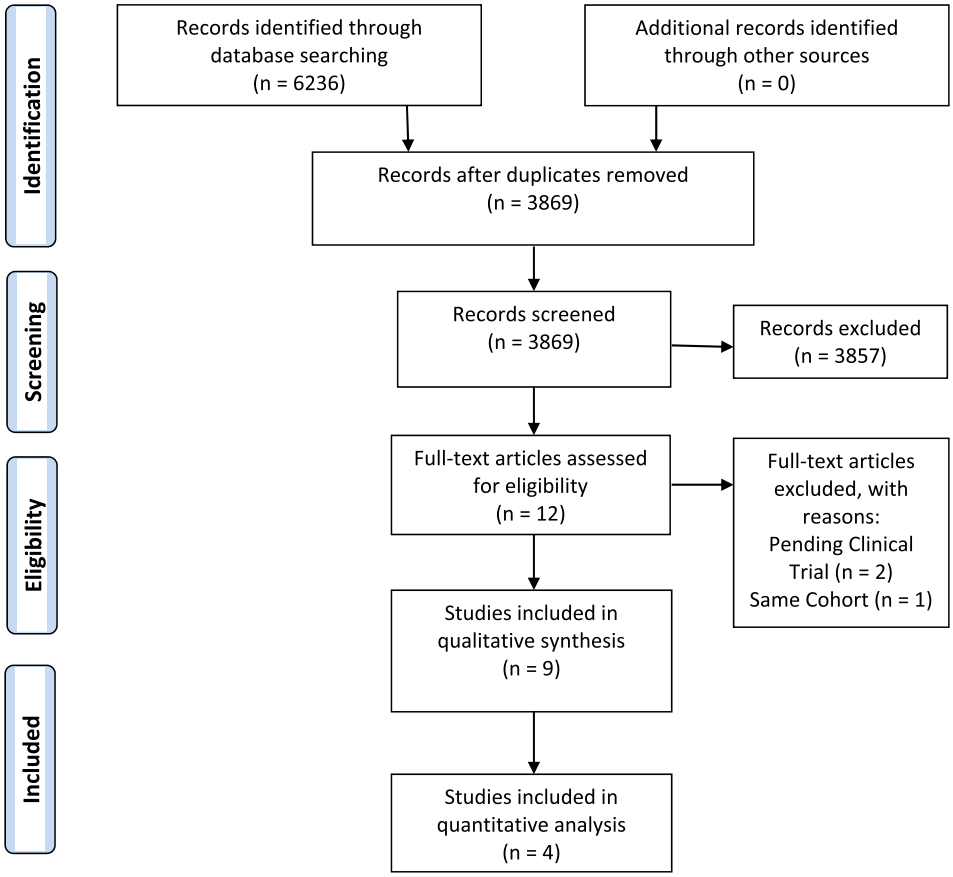

Fig. 1. PRISMA Flow Chart of the Literature Search.
This figure details the literature search of 7 databases from the inception of the database until through May 31, 2019. 6236 records were screened, including 3869 unique records, 9 of which were included in the systematic review, and 4 were included in the meta-analysis.

comparing treatment to the baseline measurements of the treatment group.

3. Results

3.1. Literature search

Six thousand two hundred and thirty-six results were identified by our search strategy. After removal of duplicates, there were 3869 unique records screened by title and abstract. 12 articles underwent full-text review and of which 2 were excluded for being pending studies, and 1 was excluded being a duplicate cohort. Therefore, 9 studies were included in the systematic review, 4 of which were included in the meta-analysis.[26,42–49] A PRISMA flow-chart is included in Fig. 1.

3.2. Study characteristics and findings

Study characteristics and findings are summarized in Table 1. Of the 9 included studies, 4 were RCTs,[44–46,49] and 5 were case series.[26,42,43,47,48] All included studies were published between 2014 and 2019.4 studies were conducted in Europe,[26,42,46,47] 4 in Asia,[43–45,49] and 1 in North America.[48]

Results included the efficacy of intra-articular PRP injections for osteoarthritis of the hand,[26,46,47] ankle,[42,43] and for talar osteochondral lesions,[44,45,49] and Sampson et al. examined the effects of PRP on multiple joints including the ankle.[48] Controls included intra-articular hyaluronic acid (HA),[44,49] saline,[44] and corticosteroids.[46] One study utilized a control of surgery without injections in their examination of PRP as an adjunct to surgery.[44] Diagnosis and grading of osteoarthritis was established using joint-appropriate radiographic criteria and clinical presentation (Table 1). Table 2 summarizes the alternative methods for PRP preparation and administration between studies. 7 studies reported using LP-PRP, and 2 studies did not report on the leukocyte status of the PRP.[44,45] 2 studies activated PRP with calcium chloride,[43,49] and the mean number of treatments was 2 (range: 1–4) separated by 1–2 weeks.

3.3. Risk of Bias Assessment

Cochrane risk of bias analysis (Fig. 2) of the RCTs demonstrated that 3 studies had a high risk of bias,[45,46,49] and 1 study had a low risk of bias.[44] All studies reported on conflicts of interest or sources of funding, and only 1 study reported having an author who is an industry-related expert advisor.[26]

3.4. Meta-analysis

Our meta-analysis includes 4 RCTs and shows that PRP effectively improves pain and function when measured at both short-term follow-up defined as fewer than 6 months post-treatment, and at long-term follow-up, defined as 6 months or longer since treatment. For improving function, when compared to control, the results show that PRP is superior to control in improving function at long-term follow-up (Fig. 3 $p = 0.0004$) and short-term follow-up (Fig. 4 $p < 0.02$). For improving pain, when compared to control, PRP is superior to control at long-term follow-up (Fig. 5 $p < 0.01$). Although the improvement of pain from PRP treatment was not significantly different from control at short-term follow-up (Fig. 6 $p < 0.51$), there was still a significant improvement following treatment with PRP compared to the baseline values at the time of treatment (Fig. 7 $p < 0.00001$). Significant

Table 1
Study details and findings.

Author, Year	Study Type, Cohort Size	Control	Osteoarthritis Classification	Outcomes	Improvements at Follow-up
Malahias et al.[46] 2018	RCT, n = 33	Methylprednisolone with lidocaine (17 patients)	Grade IV Eaton and Littler	VAS pain: Improved ($p < 0.05$) QDASH: Improved ($p < 0.05$) Patient Satisfaction: Improved ($p < 0.05$) Adverse Effects: None occurred	Compared to control: No change at 3 months, significantly improved at 12 months
Mayoly et al.[47] 2019	Case-series, n = 3	–	Grade IV Kellgren Lawrence	VAS pain: Improved DASH: Improved PRWE: Improved Patient Satisfaction: Satisfied or Very Satisfied	Improved at 3, 6, and 12 months
Loibl et al.[26] 2016	Case-series, n = 10	–	Grade II/III/IV Eaton and Littler	VAS pain: Improved ($p < 0.05$) Mayo Wrist Score: Improved ($p < 0.05$) Strength measures: No change DASH: No change Adverse Effects: 1 auto-resolving wrist ganglion	Significantly improved at 3 and 6 months
Sampson et al.[48] 2016	Case-series, n = 125 (ankle n = 6)	–	Grade III or IV Kellgren Lawrence	VAS pain: Improved Patient Satisfaction: median 9.0/10.0 Adverse Effects: None occurred	Follow-up mean 148 day, minimum 56 day
Mei-Dan et al.[49] 2012	RCT, n = 30	Hyaluronic Acid (15 patients)	Grade 1/2a/2b/3 Ferkel	VAS pain: Improved VAS stiffness: Improved ($p < 0.05$) VAS function: Improved ($p < 0.05$) AHFS: Improved ($p < 0.05$) Adverse Effects: 1 patient reported mild pain resolving spontaneously by week 3	Significantly improved as compared to control at 4, 12, and 28 weeks
Görmeli et al.[44] 2015	RCT, n = 40	Hyaluronic acid (14 patients), Saline (13 patients)	Grade II/III/IV Hepple	VAS pain: Improved ($p < 0.05$) AOFAS: Improved ($p < 0.05$) Patient Satisfaction: 61.5% satisfied Adverse Events: None reported	Significantly improved at postop time as compared to control, improved patient satisfaction at 1 year
Guney et al.[45] 2016	RCT, n = 54	Microfracture (19 patients), Mosaicplasty (13 patients)	Grade II/III/IV Hepple	VAS Pain: Improved ($p < 0.05$) AOFAS: Improved ($p < 0.05$) FAAM: Absent baseline data; no intergroup differences at endpoint	No differences between groups at last follow-up median 42 months (range: 12–84)
Fukawa et al.[43] 2017	Case-series, n = 20	–	Stage 2/3a/3b/4 Tanaka-Takakura	VAS pain: Improved ($p < 0.05$) JSSF Ankle/Hindfoot Scale: Improved ($p < 0.05$) SAFE-Q: Improved ($p < 0.05$) Adverse Events: 1 patient had mild pain and swelling resolved within 2 days	Significantly improved VAS and JSSF scores at 4, 12, and 24 weeks. Significantly improved SAFE-Q at 12 weeks.
Repetto et al.[42] 2017	Case-Series, n = 20	–	Stage 3/4 Kellgren Lawrence	VAS pain: Improved ($p < 0.05$) FADI: Improved ($p < 0.05$) Patient Satisfaction: 80% satisfied Adverse Events: None reported	Significantly improved VAS and FADI at mean 18 month follow-up (range: 12–30)

RCT: Randomized Controlled Clinical Trial. VAS: Visual Analog Scale. DASH: Disabilities of Arm and Shoulder. AHFS: Ankle-Hindfoot Scale. FAAM: Foot and Ankle Ability Measure. AOFAS: American Orthopaedic Foot and Ankle Society scoring system. JSSF: Japanese Society for Surgery of the Foot. SAFE-Q: Self-Administered Foot Evaluation Questionnaire. FADI: Foot and Ankle Disability Index.

Table 2
PRP preparation and administration.

Author, Year	Application Site	Platelet Concentration vs Baseline Leukocyte Status	Number of Treatments	Injection Interval (days)	Application Method	Platelet Activation	Centrifugation Procedure
Malahias et al.[46] 2018	CMC joint	2.6 Leukocyte-poor	2	15	Ultrasound guided	–	1st centrifugation: 3100 rpm 2nd centrifugation: 3100 rpm Total time centrifuged: 10 min
Mayoly et al.[47] 2019	Radiocarpal joint	2 0.04% (± 0.04%) Leukocytes	1	–	X-ray guided PRP injected immediately after micro-fat injection	–	3200 rpm for 10 min
Loibl et al.[26] 2016	TMC joint	2.4 Leukocyte-reduced	2	14	Fluoroscopic guidance	–	1500 rpm for 4 min
Sampson et al.[48] 2016	Ankle, knee, hip, cervical spine, shoulder	4.2 Low leukocyte	1	–	Bone marrow concentrate was injected intra-articular 8 weeks before PRP	–	1st centrifugation: 2800 rpm for 10 min 2nd centrifugation: 3400 rpm for 6 min
Mei-Dan et al.[49] 2012	Talus	2–3 No Leukocytes	3	14	–	Calcium Chloride	640 g for 8 min
Görmeli et al.[44] 2015	Talus	5.2 Not Reported	1	–	PRP injected 24–36 h post-microfracture at time of Hemovac drain removal	–	–
Guney et al.[45] 2016	Talus	5.4 Not Reported	1	–	PRP injected 6–24 h post-microfracture at time of Hemovac drain removal	–	–
Fukawa et al.[43] 2017	Ankle	5.1 Leukocyte Poor	3	14	Ultrasound guided	Calcium chloride	1st centrifugation: 800 g for 5 min 2nd centrifugation: 1500 g for 8 min
Repetto et al.[42] 2017	Ankle	2–3 Low (< 1000 leukocytes/μL)	4	7	–		1st centrifugation: 3550 rpm for 12 min 2nd centrifugation: 1100 rpm for 10 min 3rd centrifugation: 2600 rpm for 20 min

CMC = Carpometacarpal. TMC = Trapeziometacarpal.

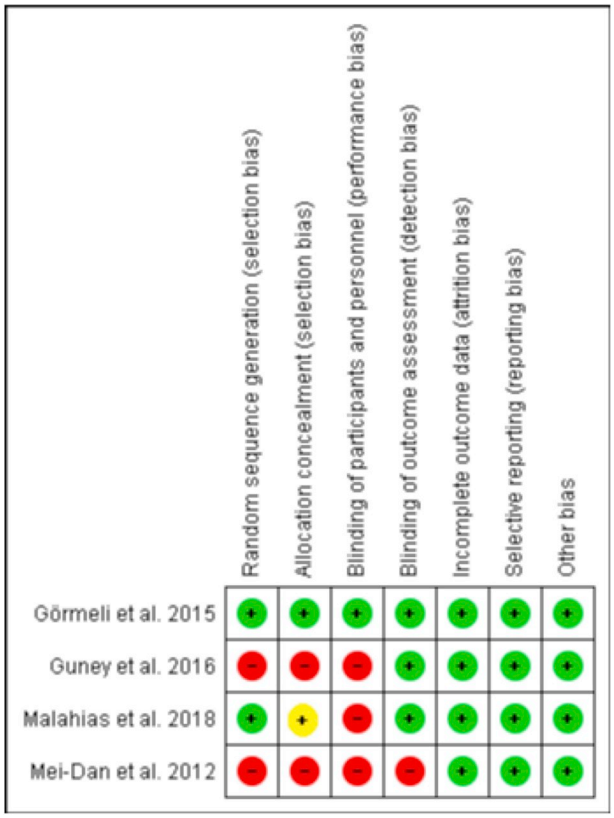

Fig. 2. Cochrane Risk of Bias Assessment of Randomized Controlled Trials. Four studies assessed for bias included 3 studies with high risk of bias, and 1 study with low risk of bias.

heterogeneity was present in the meta-analysis of pain due to the inclusion of Malahias et al., who reported values with interquartile range, thereby the conversion to standard deviation provided an acknowledged source of heterogeneity.

4. Discussion

4.1. Osteoarthritis of the hand and wrist

Pain and a decline of function are the most common manifestations of osteoarthritis in the small joints of the hands and wrists. As inflammation and degeneration progresses, patients develop joint deformity and debilitating stiffness. Symptomatic control with NSAIDs and intra-articular corticosteroid injections has been the mainstay of treatment, but it fails to halt disease progression and many physicians and patients desire a method of restoring the joint integrity and function.

Focusing on potential curative or restorative therapies, Loibl et al. in a 2016 small pilot study of ten patients used two injections of PRP into the trapeziometacarpal (TMC) joint over four weeks to treat patients with osteoarthritis. They found a significant ($p < 0.05$) improvement in both VAS pain and MAYO wrist scores, however, no improvement in functional DASH scores at six months of follow-up.[26] These results are supported by a small 2019 study by Mayoly et al. showing that in three patients with severe osteoarthritis (Kellgren-Lawrence stage four), one PRP and mixed micro-fat preparation injection into the wrist reached a Minimally Clinically Important Difference (MCID) for DASH score in all three patients, and a MCID in VAS pain for two out of three patients when followed up at one year.[47] Both of these studies are limited by the small sample size and a lack of control groups.[50]

Malahias et al. conducted a 2018 RCT with thirty-three patients with grade I-III Eaton and Littler osteoarthritis of the TMC joint, comparing outcomes at three and twelve months between patients who received two intra-articular PRP injection two weeks apart and control patients who received two intra-articular methylprednisolone and lidocaine injections two weeks apart. While patients in the corticosteroid and anesthetic group had good relief of pain in the first weeks, at twelve month follow-up, the group that received PRP had significantly improved VAS, Q-DASH and subjective satisfaction with the procedure when compared to controls ($p < 0.025$).[46]

The majority of guidelines for recommended treatments at this time are supportive and conservative. Steroid injections have shown some benefit, and therefore many physicians use them as a cornerstone of their practice.[51] However, while they provide symptomatic relief, there are drawbacks including a short-lasting effect and several relative contraindications including diabetes mellitus and immunosuppression.[52]

4.2. Osteoarthritis of the foot and ankle

While estimates of the rates of osteoarthritis of the feet and ankles vary widely, a review of the literature by Murray et al. demonstrated that around 5% of adults over the age of 50 had osteoarthritis in their ankles.[53] As weight bearing becomes painful, the quality of life for these patients is greatly affected. Fukawa et al., in a case series of 20 patients, demonstrated the efficacy of three PRP injections into the ankles separated by two-week intervals. The patients had significantly improved pain and function scores by JSSF, VAS and SAFE-Q ($P = 0.04$) at 24 weeks post treatment, although pain reduction peaked at 12 weeks.[43] When comparing PRP versus HA injections, a 2012 RCT found that PRP was significantly better than HA for treatment of osteochondral lesions of the talus, with superior improvement in pain and function at 6 months.[49] A 2017 retrospective study by Repetto et al. found that at 17 months, patients who received four intra-articular PRP injections over the course of four weeks, had a significant reduction in VAS with a positive effect on function ($p < 0.001$), and 80% of patients were satisfied or very satisfied.[42]

The effects of PRP have also been evaluated in patients who have had surgery. Two studies published examined the effects of PRP in patients who received microfracture surgery of the talus. In 2015, Guney et al. published a RCT containing 35 patients that showed intra-articular PRP provided improvement in functional status ($p = 0.001$) and VAS pain ($p = 0.001$) at 16 months, despite having controls who had significantly less pain at baseline ($p = 0.014$).[54] Görmeli et al., in

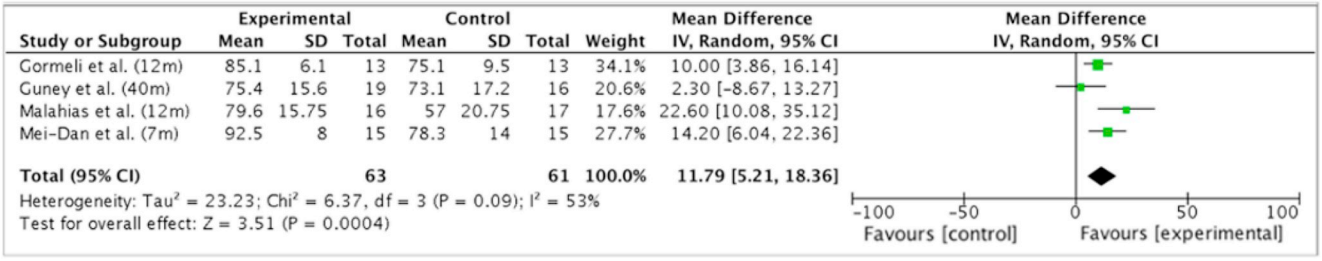

Fig. 3. Random effects forrest plot comparing PRP and control for function at long-term follow-up.

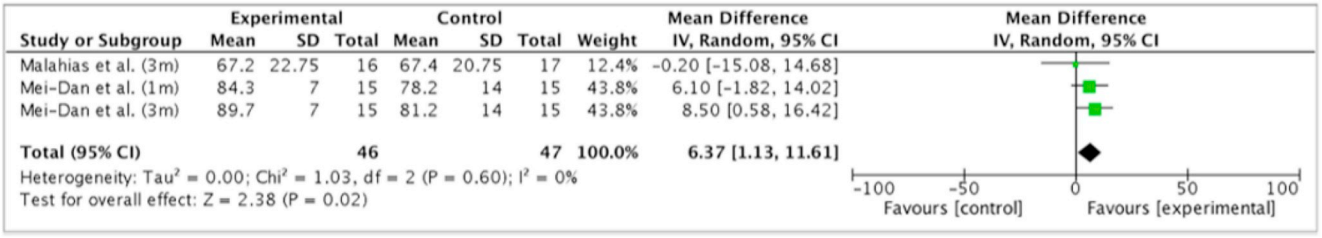

Fig. 4. Random effects forrest plot comparing PRP and control for function at short-term follow-up.

2015, in a RCT of 40 patients, also examined PRP after microfracture repair of talar osteochondral lesions, where they compared adjunct PRP versus HA versus saline intra-articular injections and found that PRP resulted in the greatest subjective improvement in functional status in addition to the greatest reduction in VAS pain ($p < 0.005$) at average 15-month follow-up.[44]

Other attempts at using PRP in conjunction with biologic molecules include a 2016 study by Sampson et al. who showed that in 125 patients, eight weeks after initial injection of autologous bone marrow aspirate, PRP injection resulted in a significant decrease in VAS pain scores at twenty weeks follow-up. However, the effect was less pronounced in non-weight bearing joints than in weight-bearing joints.[48]

4.3. Cartilage regeneration

Chondrocyte expression of ribonucleic acid (RNA) and proteins varies both by the presence of osteoarthritis pathology as well as by the region of the body.[13] The reparative and regenerative potential of a cartilaginous joint is position-dependent, with the small joints of the hands and feet having the most potential.[13] Although many studies included pre-treatment diagnostic imaging such as ultrasound, X-ray, CT scan, and MRI, there were no studies utilizing a post-treatment imaging. As such, further clinical trials are needed to examine whether PRP produces a measurable regeneration of cartilage or a cessation to cartilage degeneration.

The current evidence provided by our meta-analysis, whereby comparison of PRP to control was superior in reducing pain only in long-term follow-ups, lends to provide support to the idea that the components of PRP may stimulate chondrocyte activity to provide a regenerative effect on the pathology of the joint.

Future studies investigating a regenerative potential of PRP on cartilage should bear in mind that multiple treatments appear to be preferred for providing additive benefits when treating small joint osteoarthritis.[26,42,43,46,49] When PRP is utilized in different applications, such as facial skin rejuvenation, skin thickness increases ranged from 10 to 290 μm as measured on ultrasound,[55,56] optical coherence tomography,[57] and biopsy.[58,59] Therefore, when examining the effect on cartilage, high resolution imaging systems will likely be needed to determine whether PRP produces a measurable effect on cartilage regeneration. Studies show benefits at 1 and 2 months after the final treatment, and the effects may continue to increase months after treatment.[55,57] Therefore, long-term follow-up of the patients in future trials is needed.

4.4. Protocols for PRP preparation and injection

Across the fields of PRP application, PRP has shown efficacy despite significant variability in centrifugation methods. Small joint osteoarthritis treatments have maintained statistical and clinical significance whether the PRP protocol calls for 1–3 centrifugations for times ranging from 4 to 42 min. Loibl et al. had the least intensive centrifugation protocol consisting of a single 4-min centrifugation at 1500 rpm, however, they disabled the brake on their centrifuge in an effort to enhance their leukocyte reduction for LP PRP.[26] Of the 7 studies that reported on leukocyte counts, 100% prepared LP PRP which is consistent with other reviews on PRP used to treat large joint or knee osteoarthritis.[21,23]

Due to the heterogeneity of PRP preparations protocols, there is an incompletely defined range at which PRP remains effective in reducing pain and increasing joint function. Most studies have platelet concentrations of two to five times greater than baseline which has been shown to have optimal effects as excessive platelet concentration can inhibit cell function.[24,60,61] Additionally, although many studies use multiple PRP injections, there is debate for whether multiple PRP injections result in better outcomes compared to a single injection.[62] Due to the short half-lives of many beneficial growth factors in PRP, it is theorized that multiple injections are needed.[37,63,64] In a 2017 RCT with 162 patients, Görmeli et al. demonstrated that multiple PRP injections significantly improved ($p < 0.05$) functional and pain scores at 6-month follow-up compared with a single PRP injection or HA for early knee osteoarthritis only.[65] Alternatively, a 2013 RCT of 78 patients by Patel et al. did not find a difference between one injection of PRP and two injections, however, this study used a concentration three times greater than is standard which may have confounded the results.[66] The use of single versus multiple PRP injections for the treatment of osteoarthritis lacks consensus on determining an optimal PRP dosage and concentration.

4.5. Confounding effects of severity

While many studies have demonstrated that PRP is more effective in early stages compared to late stages of osteoarthritis,[43,65,66] other studies looked exclusively at the effects of PRP on early osteoarthritis, limiting the amount of evidence for a comparison.[46,67] Although PRP is

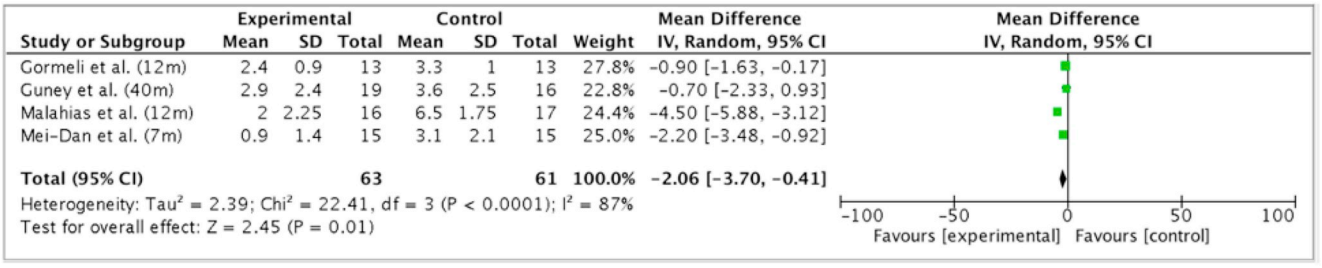

Fig. 5. Random effects forrest plot comparing PRP and control for pain at long-term follow-up.

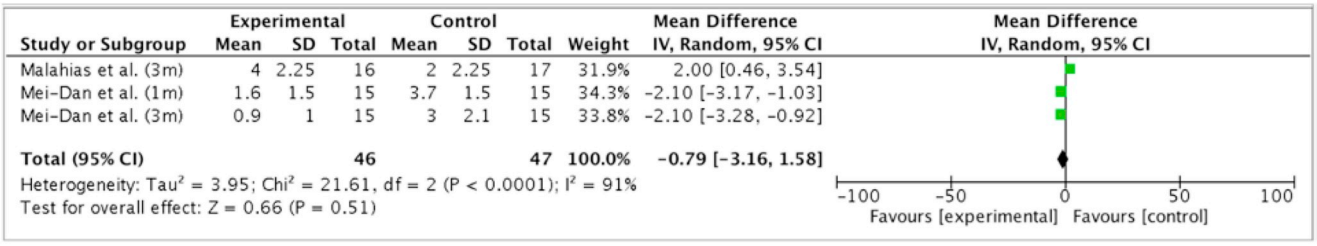

Fig. 6. Random effects forrest plot comparing PRP and control for pain at short-term follow-up.

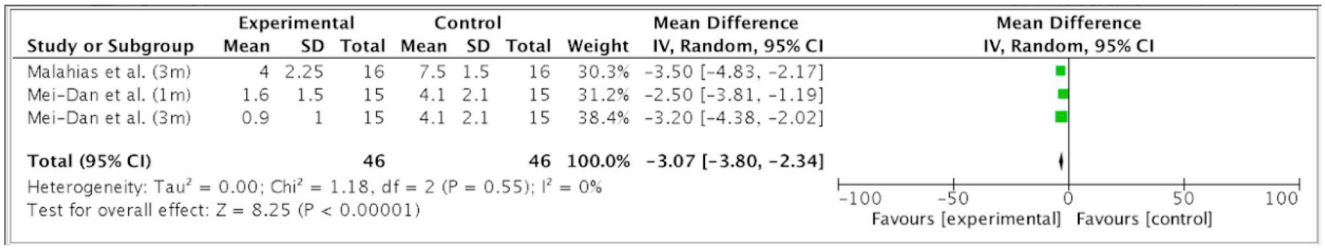

Fig. 7. Random effects forrest plot comparing PRP and baseline values of the PRP group for pain at short-term follow-up.

demonstrably effective at treating symptoms of both early and late osteoarthritis via anti-inflammatory mechanisms, it has been proposed that patients with a lower degree of cartilage injury have improved clinical outcomes due to the higher prevalence of chondrocytes and other living cells that are able to respond to growth factors in PRP.[65]

4.6. Study limitations

This study is limited by a low number of RCTs published in literature on treatment of small joint osteoarthritis, small study sample sizes, variable pathologies and grades of pathologies, heterogeneous PRP protocols and treatment evaluation methods, and non-blinded RCT study designs. Additionally, our meta-analysis of pain is limited by significant heterogeneity between the included studies. An additional limitation exists due to reporting bias of published studies.

5. Conclusion

The past decade has seen an expanding interest in applying PRP for the treatment of various musculoskeletal disorders due to its regenerative potential and bioactive factors which promote resolution of pain and tissue healing. The growing body of evidence demonstrates the utility of PRP in healing cartilage defects, promoting stem cell proliferation, and preventing chondrocyte and ECM degradation in the treatment of osteoarthritis. Our meta-analysis of RCTs shows that PRP effectively improves both pain and function in patients with small joint osteoarthritis. The data suggests that PRP may be superior to other intra-articular injections, and that the superiority of PRP in improving pain and function is magnified as the duration of follow-up increases. Evidence from a limited number of case series suggests beneficial use of PRP for the treatment of osteoarthritis pain in low grade osteoarthritis, and the RCTs reviewed indicate the benefit of PRP after surgical repair of the ankle. Larger RCTs with less heterogeneity and less risk of bias are needed to elucidate the effectiveness of intra-articular PRP injections, to make PRP a more convincing treatment option, and to delineate appropriate indications and standardized protocols.

Disclosures

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CRediT authorship contribution statement

Adam Evans: Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Maryo Ibrahim:** Formal analysis, Investigation, Resources, Writing - original draft, Visualization. **Rand Pope:** Validation, Writing - review & editing. **James Mwangi:** Investigation. **Mina Botros:** Formal analysis, Resources, Writing - original draft, Writing - review & editing. **Shepard P. Johnson:** Writing - review & editing. **Salam Al Kassis:** Conceptualization, Methodology, Supervision, Project administration.

Declaration of competing interest

None.

Appendix. Search Strategy

Cochrane Database Search

Search Number	Search Terms	Results
22	#20 AND #21	1463
21	(OR #1-#16)	131214
20	(OR #17-#19)	1130
19	((platelet-rich plasma) OR (platelet rich fibrin) OR (platelet-rich fibrin) OR (platelet gel) OR (autologous conditioned plasma) OR (prp) OR (prf) OR (prgf) OR (acp) OR (pure platelet-rich-plasma) OR (platelets)) (Word variations have been searched)	28207
18	MeSH descriptor: [Platelet-Rich Fibrin] explode all trees	42
17	MeSH descriptor: [Platelet-Rich Plasma] explode all trees	374

16	MeSH descriptor: [Foot Bones] explode all trees	254
15	MeSH descriptor: [Foot] explode all trees	1559
14	MeSH descriptor: [Visual Analog Scale] explode all trees	659
13	MeSH descriptor: [Hand Bones] explode all trees	141
12	MeSH descriptor: [Forefoot, Human] explode all trees	191
11	MeSH descriptor: [Joints] explode all trees	7656
10	MeSH descriptor: [Thumb] explode all trees	170
9	MeSH descriptor: [Hand] explode all trees	2525
8	MeSH descriptor: [Carpometacarpal Joints] explode all trees	38
7	MeSH descriptor: [Injections, Intra-Articular] explode all trees	1195
6	MeSH descriptor: [Arthritis] explode all trees	13494
5	MeSH descriptor: [Chondrogenesis] explode all trees	6
4	MeSH descriptor: [Cartilage, Articular] explode all trees	266
3	MeSH descriptor: [Joint Capsule] explode all trees	287
2	MeSH descriptor: [Osteoarthritis] explode all trees	6385
1	(Osteoarthritis) OR (synovium) OR (articular cartilage) OR (synovial joint) OR (cartilage) OR (chondrocyte) OR (chondrogenesis) OR (arthritis) OR (joint capsule) OR (intra-articular) OR (CMC) OR (MCP) OR (carpal) OR (hand) OR (wrist) OR (thumb) OR (pollex) OR (pollicis) OR (finger) OR (finger*) OR (carpometacarpal) OR (metacarpophalangeal) OR (phalange) OR (phalanx) OR (phalan*) OR (metacarp*) OR (metacarpus) OR (knuckle) OR (digit) OR (digital) OR (basal joint) OR (basal-joint) OR (carpo*) OR (trapeziometacarpal) OR (synovitis) OR (interphalangeal) OR (metatarsus) OR (hallux) OR (hallucis) OR (toe) OR (toes) OR (tarsal) OR (PIP) OR (DIP) OR (tarsometatarsal) OR (radiocarpal) OR (radius) OR (ulna) OR (ankle) OR (tarsus) OR (Rhizarthrosis) OR (VAS) OR (Eaton-Littler) OR (Michigan hand) OR (MHQ) OR (Mayo wrist) OR (distal metacarp*) OR (metatars*) OR (distal metacarp*) OR (scaphoid) OR (lunate) OR (pisiform) OR (trapezium) OR (trapezoid) OR (capitate) OR (hamate) OR (Ankle OA scale) OR (degenerative) OR (Disabilities of the Arm, Shoulder) OR (Kellegren Lawrence) OR (enthesitis) OR (enthesis) OR (enthesopathy)	126631

Ovid Medline Database Search

Search Number	Search Terms	Results
25	10 and 23 and 24	1178
24	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 1 or 2 or 3 or 4 or 5	1296025
23	1 or 2 or 3 or 4 or 5 or 11 or 12 or 13	415279
22	exp Carpometacarpal Joints/	708
21	exp Hand Bones/	11400
20	exp Hand/	82786
19	exp Thumb/	8748
18	exp Forefoot, Human/	14721
17	exp visual analog scale/	2467
16	exp Foot/	48868
15	exp Foot Bones/	16920
14	(CMC or MCP or carpal or hand or wrist or thumb or pollex or pollicis or finger or finger* or carpometacarpal or metacarpophalangeal or phalange or phalanx or phalan* or metacarp* or metacarpus or knuckle or digit or basal joint or basal-joint or carpo* or trapeziometacarpal or interphalangeal or metatarsus or hallux or hallucis or toe or toes or tarsal or tarsus or Rhizarthrosis or visual analog or VAS or Eaton-Littler or Michigan hand or MHQ or Mayo wrist or distal metacarp* or metatars* or distal metacarp* or unl* or scaphoid or lunate or pisiform or trapezium or trapezoid or capitate or hamate or Ankle OA scale or degenerative or Disabilities of the Arm, Shoulder or Kellegren Lawrence or enthesitis or enthesis or enthesopathy).mp.	1141084
13	exp Arthritis/	246941
12	exp Osteoarthritis/	58777
11	(Osteoarthritis or arthritis or chondrogenesis or synovitis).mp.	286379
10	6 or 7 or 8 or 9	157815
9	exp Platelet Activation/	47198
8	exp Platelet-Rich Plasma/	3557
7	exp Platelet-Rich Fibrin/	197
6	(platelet-rich plasma or platelet rich fibrin or platelet-rich fibrin or platelet gel or autologous conditioned plasma or prp or prf or prgf or acp or pure platelet-rich-plasma or platelets or platelet concentrate).mp.	140322
5	exp Joint Capsule/	27673
4	exp Chondrogenesis/	4734
3	exp Cartilage, Articular/	27883
2	exp Injections, Intra-Articular/	7442
1	(synovium or articular cartilage or synovial joint or cartilage or joint capsule or intra-articular).mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	

Ovid Embase Database Search

Search Number	Search Terms	Results
25	10 and 23 and 24	1839
24	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 1 or 2 or 3 or 4 or 5	1602385
23	1 or 2 or 3 or 4 or 5 or 11 or 12 or 13	593085
22	exp Carpometacarpal Joints/	1802
21	exp Hand Bones/	13233
20	exp Hand/	73177
19	exp Thumb/	8712
18	exp Forefoot, Human/	4311
17	exp visual analog scale/	77170
16	exp Foot/	53488
15	exp Foot Bones/	19027

14	(CMC or MCP or carpal or hand or wrist or thumb or pollex or pollicis or finger or finger* or carpometacarpal or metacarpophalangeal or phalange or phalanx or phalan* or metacarp* or metacarpus or knuckle or digit or basal joint or basal-joint or carpo* or trapeziometacarpal or interphalangeal or metatarsus or hallux or hallucis or toe or toes or tarsal or tarsus or Rhizarthrosis or visual analog or VAS or Eaton-Littler or Michigan hand or MHQ or Mayo wrist or distal metacarp* or metatars* or distal metacarp* or unl* or scaphoid or lunate or pisiform or trapezium or trapezoid or capitate or hamate or Ankle OA scale or degenerative or Disabilities of the Arm, Shoulder or Kellegren Lawrence or enthesitis or enthesis or enthesopathy).mp.	1422375
13	exp Arthritis/	434746
12	exp Osteoarthritis/	119919
11	(Osteoarthritis or arthritis or chondrogenesis or synovitis).mp.	432615
10	6 or 7 or 8 or 9	158655
9	exp Platelet Activation/	26727
8	exp Platelet-Rich Plasma/	10937
7	exp Platelet-Rich Fibrin/	502
6	(platelet-rich plasma or platelet rich fibrin or platelet-rich fibrin or platelet gel or autologous conditioned plasma or prp or prf or prgf or acp or pure platelet-rich-plasma or platelets or platelet concentrate).mp.	146829
5	exp Joint Capsule/	3370
4	exp Chondrogenesis/	9898
3	exp Cartilage, Articular/	26990
2	exp Injections, Intra-Articular/	6194
1	(synovium or articular cartilage or synovial joint or cartilage or joint capsule or intra-articular).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	164182

Clincialtrials.gov Database

Total Results: 507

Condition or disease: Platelet rich plasma OR platelet rich fibrin OR platelet gel OR autologous conditioned plasma OR prp OR prf OR prgf OR acp OR platelet concentrate OR platelet rich growth factor or platelet activation OR thrombocyte rich plasma

Other terms: osteoarthritis OR thumb OR first carpometacarpal joint OR rhizarthrosis OR basal joint OR carpometacarpal OR hand osteoarthritis OR Osteoarthritis Both Hands OR Osteoarthritis Hand OR CMC OR Basal joint OR Carpometacarpal OR platelet OR Visual Analog Pain Scale OR Eaton-Littler OR Michigan hand OR MHQ OR Mayo wrist OR distal metacarp* OR metatars* OR distal metacarp* OR unl* OR scaphoid OR lunate OR pisiform OR trapezium OR trapezoid Or capitate OR hamate OR Ankle OA scale OR degenerative OR Disabilities of the Arm, Shoulder OR Kellegren Lawrence OR enthesitis OR enthesis OR enthesopathy

Web of Science Database

Total Results: 1455

Search Number	Search Terms	Results
9	#8 AND #7 AND #2	1249
8	#6 OR #1	2162127
7	#3 OR #1	495870
6	#4 OR #5	2039214
5	ALL = (Visual Analog Pain Scale OR Eaton-Littler OR Michigan hand OR Mayo wrist OR distal metacarp* OR metatars* OR unl* OR scaphoid OR lunate OR pisiform OR trapezium OR trapezoid OR hamate OR Ankle OA scale OR Kellegren Lawrence OR enthesitis OR enthesis OR enthesopathy)	564300
4	ALL = (CMC or MCP or carpal or hand or wrist or thumb or pollex or pollicis or finger or finger* or carpometacarpal or metacarpophalangeal or phalan* or metacarp* or metacarpus or knuckle or digit or basal or carpo* or trapeziometacarpal or metatarsus or hallux or hallucis or toe or toes or tarsal or tarsus or rhizarthrosis)	1521843
3	ALL = (Osteoarthritis or arthritis or chondrogenesis or synovitis)	419073
2	ALL = (platelet-rich plasma or platelet rich fibrin or platelet-rich fibrin or platelet gel or autologous conditioned plasma or prp or prf or prgf or acp or pure platelet-rich-plasma or platelet concentrate)	62428
1	ALL = (synovium or articular cartilage or synovial joint or cartilage or joint capsule or intra-articular)	136904

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