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# Efficacy and Safety of Platelet-Rich Plasma Injections for Osteoarthritis

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## Abstract

*Purpose of the review* Therapeutic options for the treatment of osteoarthritis (OA), the most common type of arthritis, are limited, leaving many patients symptomatic and resulting in extensive disability and economic cost. Platelet-rich plasma (PRP) has become a therapeutic treatment offered by a number of practitioners for the management of a variety of conditions from osteoarthritis to wound healing, dental procedures, soft tissue injuries, and alopecia. As PRP is a blood product rather than a pharmaceutical agent and is often administered autologously, it has not undergone standard pharmaceutical approval processes. However, the use of PRP has thus far been grandfathered in jurisdictions such as Canada due to its wide use for many years. As a result, the clinical utilization of PRP for osteoarthritis has extended rapidly despite largely heterogeneous and often inconclusive studies of its efficacy.
*Recent findings* In the last year, studies with a higher level of evidence have been published that indicate that PRP may result in improved pain and function at later timepoints (e.g., 6 and 12 months) compared with either hyaluronic acid or saline.
*Summary* This review will provide updated information of the scientific basis, clinical studies, and future studies of PRP.

## Introduction

Osteoarthritis (OA) is a serious, often debilitating condition currently ranked as the 11th highest contributor to global disability based on data from the 2010 Global Burden of Disease Study [1]. The most common type of arthritis, OA, is reported to have a global age-standardized prevalence of 3.8% and 0.85% for knee and hip OA respectively [1]. Knee and hip OA can result in chronic pain, immobility, and functional disability and has been shown to be associated with excess mortality [2, 3]. OA is also associated with substantial direct, indirect, and intangible economic costs [3, 4]. Evidence-based treatment guidelines for knee and hip OA vary somewhat between organizations [5–8]. Non-surgical interventions such as exercise, strength training, weight management, self-management programs, acetaminophen, non-steroidal anti-inflammatory drugs (oral or topical), oral COX-2 inhibitors, duloxetine, or corticosteroid injections are supported by studies of a good level of evidence [8].

There are currently no recommended disease-modifying therapeutic options for osteoarthritis. Recently, practitioners have started using a number of newer therapies in an attempt to fill this therapeutic void despite currently lacking sufficient evidence to support their use: intra-articular platelet-rich plasma (PRP) injections are being used as a treatment for knee and hip OA, as are other injected therapies including prolotherapy, hyaluronic acid, and stem cell therapy. The most recent Osteoarthritis Research Society International (OARSI) guidelines recommended strongly against PRP and intra-articular stem cell therapy given the low quality of evidence and lack of standardization of the formulations [8]. Similarly, the American Association of Hip and Knee Surgeons, Hip Society, and Knee Society has recently published a position statement indicating that they cannot currently recommend either PRP or intra-articular stem cell therapy for advanced knee or hip OA [9]. Research into PRP injections for OA has been expanding with in vitro, in vivo, and clinical studies being published along with a number of meta-analyses. The mechanisms of action and efficacy of PRP have thus far been difficult to assess due to the heterogeneity of techniques for the preparation and administration of PRP, as well as the varied study designs utilized in their research. This review will provide an updated discussion of the basic science and clinical studies with a focus on the most recent publications.

# Osteoarthritis pathophysiology: a complex disease

OA has been historically described as symptomatic joint pain in the presence of radiographic changes including joint space narrowing, osteophytes, bone sclerosis, and joint deformity. Studies of OA pathophysiology indicate a complex interplay between molecular, mechanical, and inflammatory changes resulting in cartilage degradation, synovitis, neuropathic pain, and osteophyte development. Felt to be a heterogeneous disease, a variety of OA phenotypes have been proposed so as to improve disease classification and potentially improve future studies of pathophysiology and therapeutics [10]. Factors identified that may modulate disease phenotype include radiographic severity, body mass index, inflammation, muscle strength, and comorbidities [10]. A subset of OA patients may have post-traumatic OA (PTOA) resulting from a joint injury (~ 12%), while others may have "metabolic OA" resulting from obesity or body composition [11, 12]. There are also genetic contributions to some forms of OA, but results from twin studies indicate that such contributions may be influenced by environment or epigenetic variables as studies of identical twins indicate discordance between twin pairs in disease incidence [13, 14]. Finally, hormones may also influence OA incidence as demonstrated by an increased female to male prevalence of hip OA of ~ 2:1 in post-menopausal women compared with

1:1 in premenopausal women [15]. However, the exact nature of loss of hormones on osteoarthritis development remains unclear [16].

On a molecular level, OA was once considered a disease of articular cartilage. However, it is clear that OA is a disease of the whole joint [17, 18]. Given the heterogeneity of OA discussed above, the involvement of several joint tissues in the disease process (cartilage, menisci, bone, ligaments, synovium, fat pads), it has been difficult to identify potential molecular targets to intervene in the initiation and progression of the condition. Thus, there may be multiple molecular ways in which to develop advanced OA and the need for a total joint replacement. While considerable effort has been spent on preclinical models, most of these have been post-traumatic injury OA, and although they have provided insights into the complex interactions between biology, biomechanics, and function, most of the molecular insights have not translated well to the human disease(s). However, it has become clearer that the old perspective of OA as strictly a degenerative disease of aging is not correct, and the disease process for at least some forms of the disease involves inflammatory processes ([12]; reviewed in [19, 20]) and metabolic derangements [11, 12].

As articular cartilage does not functionally repair by itself, a number of non-surgical and surgical interventions to facilitate repair or improve function have been trialed with variable results. These include hyaluronic acid (HA) injections (which are no longer endorsed by the American Academy of Orthopaedic Surgeons [6] but are conditionally recommended by the Osteoarthritis Research Society International [8]), chondrocyte transplantation [21], microfracture of the subchondral bone [22], mesenchymal stem cells (MSC) and tissue engineering [23], free MSC (allogeneic or autologous) from a variety of tissue sources [24], PRP [25], or exercise programs such as the GLA:D (Good Life with osteoArthritis in Denmark) program [26–28]. While some improve function (exercise), others improve pain scores (most patients appear with progressive pain and functional disability) [25, 26], but most address symptoms and do not initiate repair of damaged cartilage in OA patients with advanced disease. The studies by Shimomura et al. [23] indicate that tissue-engineered constructs with autologous MSC are able to contribute to cartilage defect repair (a condition which will lead to OA development) in a pilot study with patients, but whether the approach will reverse cartilage damage in early or moderate OA and restore joint function is still to be determined.

## Platelet-rich plasma: history and classification

Platelets and other blood extracts such as fibrin have been researched and used for decades for wound healing and a host of other diverse indications such as bone grafting in oral maxillofacial surgery [29], alopecia [30], and musculoskeletal and soft tissue injuries [31] with mixed results. Produced by the centrifugation of whole blood, platelet-rich plasma (PRP) is not a traditional pharmaceutical agent and thus has not been investigated or approved via standard pharmaceutical regulatory mechanisms [32–34]. As a result of not having to fulfill traditional pharmaceutical regulation protocols, the utilization of this product has become widespread and has grown more rapidly than the data to support its use in clinical practice. Although studies have been done using allogenic PRP from donors [35], PRP is most often utilized in an

autologous form produced after centrifugation of a patient's whole blood and extraction of a platelet-rich fraction. A number of different commercial systems have been derived for the production of PRP [30], but due to differences in the mechanisms of preparation (e.g., centrifugation speed, number of centrifugations, and type of anticoagulant), the resultant PRP products can differ greatly. The term PRP describes a platelet extract containing a higher concentration of platelets than autologous blood, but due to the heterogeneity of the different PRP products, a number of classification systems have been proposed to more specifically describe the properties of different PRP preparations (reviewed in [36, 37]). Variables include, for example, platelet concentration, presence of a platelet activation factor, and leukocyte concentration [36]. Following centrifuge of whole blood, the platelet-rich supernatant is removed with or without the leukocyte-rich buffy coat layer resulting in PRP that is either high or low in leukocyte concentration, termed leukocyte-rich (LR-PRP or L-PRP depending on the author) and leukocyte-poor or pure (LP-PRP or P-PRP) PRP respectively [38, 39]. For the purposes of this review, we will refer to these as L-PRP and P-PRP.

## Platelet-rich plasma basic science: what is known and some hypotheses

Osteoarthritis treatments have often attempted to replace or mimic a joint's natural components (e.g., hyaluronic acid injections or oral glucosamine and chondroitin) in hopes of recreating joint health in what are relatively poorly healing structures. PRP was first used with the belief that the fibrin and constituent blood components would improve bone healing for grafting but soon was adapted to be used in osteoarthritis treatment via intra-articular and occasionally intra-osseous injections. The proposed biologic activity of PRP is thought to be related to the action of the different blood components present including platelets, growth factors, fibrinogen, and leukocytes interacting with joint tissues in hopes of promoting repair and diminishing inflammation. Reports on the makeup of PRP have been somewhat variable and likely depend on the preparation of the PRP itself [40].

A number of studies have described the makeup of different PRP preparations. In their comparison of the constituents of different platelet and bone marrow extracts, Ziegler et al. found that P-PRP contained higher levels IL-1 receptor antagonist and matrix-metalloproteinases-2, 3, and 12 as its comparators, whereas leukocyte-containing R-PRP contained higher concentrations of some growth factors (transforming growth factor-beta [TGFβ], VEGF, endothelial growth factor [EGF], platelet-derived growth factor [PDGF]), soluble CD-40 ligand, and matrix-metalloproteinase-1 (MMP-1) [38]. Xu et al. performed a comparison of L-PRP and P-PRP and found that leukocyte-containing L-PRP had higher levels of the inflammatory cytokines IL-1β and TNF-α compared with whole blood while P-PRP had lower levels compared with whole blood [39]. In Xu's study [39], both L-PRP and P-PRP contained similar amounts of the platelet-derived growth factors PDGF-AB and TGF-β1 and the level of these growth factors correlated with the concentration of platelets in the extract. Another study of a twice-centrifuged P-PRP by Amable et al. [41] also found

higher levels of PDGF, TGF, and EGF as well as the interleukins (IL) IL-4, IL-8, IL-13, IL-17, tumor necrosis factor (TNF)-α, and interferon (IFN)-α in P-PRP compared with plasma with the degree of increase dependent on, in some cases, whether or not the P-PRP was activated with calcium chloride with or without thrombin.

Research has been conducted both in vitro and in vivo regarding the effect of PRP on joints and joint tissues or cells. A systematic review performed from 2012 to 2017 by Fice et al. [42] examined basic science studies (in vivo, in vitro, or both) assessing the effect of PRP on cartilage. As had been found in prior reviews, the assessed studies were heterogeneous in both their reported PRP preparation methods and their reported outcomes. Where studied, PRP resulted in increased cell viability of in vitro cell cultures and increased cell proliferation. A small number of studies reported increased cell migration and differentiation in vitro. There were mixed results with respect to in vitro collagen II or proteoglycan production. In vivo studies of cartilage repair described mixed results with respect to gross cartilage repair although 12 of 16 studies described improved cartilage quality under histologic studies. More recent in vivo studies include a number of OA animal models that indicate that PRP injections may be associated with less synovitis or synovial thickening than control groups [43–45], and one study indicated that synovial scores may be improved by multiple injections vs a single injection of PRP [45]. Interestingly, this same study found no significant difference in mean articular scores at the same timepoint [45].

Based on the large number of preclinical studies and some in vitro studies with human explants and cells, PRP may function in vivo to address pain and to exert an anti-inflammatory effect on the environment of the joint [46]. While pain is the usual presentation symptom, it is clear that there are different types of pain (peripheral, central, neuropathic), so the effectiveness of PRP in this regard may be variable. Furthermore, some patients can present with severe pain but are found to have little pathology on imaging, while others can present with little pain but have significant evidence of damage on imaging. In addition, pain can be influenced by the placebo effect, so appropriate comparators are needed when assessing the effectiveness of PRP injections.

## Clinical studies of platelet-rich plasma in knee osteoarthritis

The number of clinical studies on PRP in knee osteoarthritis has been rapidly increasing and a number of meta-analyses have been performed [25, 47–49]. At the time of the writing of this review, 90 studies of PRP and osteoarthritis are registered with clinicaltrials.gov. Twenty-nine are reported as having been competed, but only 4 are listed as having results, which raises concerns about the possibility of publication bias. The limited number of reported studies has also limited the ability to adequately asses the data on the efficacy of PRP in OA. In the largest of the abovementioned meta-analyses, Han et al. analyzed 15 randomized controlled trials published before April 2018 comparing intra-articular PRP with hyaluronic acid (HA) injections in knee OA [25]. Most studies included in their analysis were of repeated joint injections spaced between 1 week and 1 month apart. No significant difference was found in

participant pain scores (WOMAC pain and VAS pain) or function scores (WOMAC total, WOMAC function, or International Knee Documentation Committee [IKDC]) between PRP and HA at 1 and 3 months post injection [25]. At later timepoints (6 and 12 months), however, there was a significant reduction in the same pain and function scores when comparing PRP with HA.

Lin et al. recently published a randomized, double-blind trial comparing a single P-PRP intra-articular injection with a single hyaluronic acid injection or a normal saline sham control injection [50••]. All three groups of this adequately powered trial showed improved mean WOMAC and IKDC scores at 1 month post injection, but only P-PRP showed sustained significant WOMAC improvements up to and including the 12-month follow-up whereas the HA and saline groups did not show significant improvements from their baseline scores after the 1-month assessment [50••]. Moreover, the degree of change in the WOMAC scores is considered clinically significant based on the minimal clinically important difference (MCID) for this scoring system (reviewed in [51]). The strength of this study, in particular, is that it includes a saline sham control arm. Previous meta-analysis has shown that intra-articular saline injections themselves can lead to both statistically and clinically meaningful differences in knee OA outcomes including the total WOMAC score and the VAS pain score [52], emphasizing the need for these in studies of injectable therapies for OA. Actively enrolling patients at the time of this review, the RESTORE trial will also provide a randomized, triple-blind comparison of 3 weekly injections of either normal saline or P-PRP once reported [53].

Another recent randomized, double-blind, adequately powered study by Di Martino [54••] compared three weekly injections of either R-PRP or hyaluronic acid in knee OA (Kellgren-Lawrence grade 0–3 [reviewed in [15]]). Using the IKDC subjective outcome, both therapies improved IKDC scores, but there was no significant difference detected when comparing hyaluronic acid with PRP with the exception of a lower reintervention rate in the PRP group at 24 months which was not sustained at the end of the 64-month trial [54••].

A randomized but unblinded study by Buendia-Lopez et al. compared a single P-PRP injection (5 ml) with a single HA injection (2 ml) vs an oral NSAID treatment for up to 52 weeks [55]. Outcomes included WOMAC and VAS pain scores as well as X-ray and MRI studies. The WOMAC pain scale was significantly improved by P-PRP at both 26 and 52 weeks compared with both oral NSAIDs and HA injections. No significant difference was detected in either Kellgren-Lawrence grading or cartilage thickness seen on MRI at 12 months. These results differ from those of a phase II randomized study comparing three injections of PRP with three HA injections all given at 4-week intervals in patients with MRI-defined OA. The imaging outcomes of this study utilized an MRI grading scale (Shahriaree Classification System—modified) and indicated that there were significantly more patients achieving a greater than one grade improvement at 6 months following the injection series [56].

Undoubtedly, studies of PRP have thus far been limited by heterogeneity of techniques, protocols, and outcomes, and the subsequent meta-analyses have found mixed results. The success or "failure" of PRP to influence OA may depend in part on the type of OA a patient may have (e.g., "idiopathic," PTOA, metabolic OA, post-menopausal), as well as the quality of the components of the PRP preparations used. Studies indicate that PRP contents and their

resultant influence on chondrocytes may be influenced by the age and the presence of osteoarthritis of the donors [57]. It may become evident in future studies that other patient or donor factors such as exercise, drugs the patients are taking, and nutrition could also exert an impact on the materials included in PRP prepared in a standard manner. Finally, another factor that was never reported in the published studies is the time of day the PRP was prepared and injected. Thus, hormonal variables associated with circadian rhythms could potentially impact the quality of the PRP or its effectiveness.

One additional area that likely needs more consideration regarding PRP use in OA is that of "responders" and "non-responders." This concept has not received much attention with regard to PRP, but certainly responders and non-responders to other interventions such as corticosteroid (GC) injections [58] and HA injections [59, 60] have been noted. However, in contrast to GC and HA injections, in the case of PRP, it is not clear whether the PRP itself is responsible for the non-responsiveness or whether the context in which it is being used (e.g., patient genetics/epigenetics or the type of OA involved) leads to the observed lack of a detectable response. Future studies should take this into account by allowing for subgroup analyses to determine whether there is a subset of patients in which there is a higher likelihood of response to PRP or to assess responder rates such as those described in Pham et al. [61].

Relevant to the above discussion, recently, Dr. Rob Burnham has determined that the non-responder rate over 12 months to PRP in a cohort (65 patients, 55% female, K/L grade 2/3) of knee OA patients was > 50% (Dr. Rob Burnham, Physiatrist, Camrose Clinic (CAPRI); Camrose, Alberta; personal communication). The outcome measures assessed included WOMAC, pain (numeric rating scale, NRS), and function assessments. A non-responder was defined as those who did not reach a MCID (minimal clinically important difference for both the NRS (a drop in pain > 2) and the WOMAC (score drop of > 9) comparing values obtained 3 months prior to injection with values 3, 6, and 12 months post injection). However, this trial was not blinded, so potentially, the responders could also include those responding to a placebo effect. In addition, the OA patient participants were not selected for a particular subtype of OA and thus were a mix of subtypes. In the future, it will be important to standardize the criteria for defining responders and non-responders with PRP (and other interventions), such as using the OARSI responder criteria [61].

Furthermore, in the future, it will be important to determine whether the non-responders to PRP may be different from non-responders to other interventions such as HA to determine whether they can be impacted in a reciprocal manner or represent a unique subpopulation of patients that are non-responders to more than one intervention. Interestingly, in a clinical trial where hip OA patients received PRP, HA, or both, HA + PRP did not improve the effectiveness of PRP alone [62], but the number of patients involved was likely not sufficiently large enough to allow for subgroup analysis.

Regarding the safety of PRP injections, the majority of studies have been performed using autologous PRP obtained from a patient's own blood. Studies of allogenic PRP have been performed, however, utilizing donor blood to produce PRP which would presumably carry with it a small infectious risk similar to other blood products [35]. In their meta-analysis comparing PRP

with hyaluronic acid injections, Han et al. did not detect a significant difference in adverse events between the two groups [25]. Transient injection site pain, swelling, headache, and low back pain have been reported as possible adverse events in some studies [62–65].

## Future directions and questions

Given the current opioid crisis, and the potential of PRP to exert impact on pain and inflammation in knee OA, PRP may provide an additional conservative therapy for OA, a condition for which patients and clinicians are often acutely aware of the limited number of effective treatment options. However, there is a real need to develop more informed patient selection and to be able to identify those patients who would receive the most benefit particularly given the cost of the procedure which is often paid by the patients themselves. As there are no good drug interventions or protocols to stop or reverse the joint damage resulting from OA, the use of autologous standardized PRP on appropriate patient populations (those with mild disease, those with a specific subtype of OA, males/females, age, obesity or not, etc.) may be warranted and will require better evidence in the future, possibly using experimental designs which complement the RCT strategy.

Secondly, it will be important to determine whether there are any unique joint-specific aspects of OA (e.g., knee, hip, shoulder, spine, hand) that may influence the effectiveness of PRP use. To generate such information will require good diagnostic criteria, the ability to ascertain the disease process and subtype, and joint-specific outcome measures to assess and define success. For example, a recent study in a rat model of diet-induced obesity indicated that the induction of metabolic OA in the knee and shoulder was equivalent, but OA development in the hip was somewhat different than the other two joints [66].

Thirdly, for conservative treatment of OA patients, the interplay between PRP effectiveness and the effectiveness of other interventions, such as HA, exercise, corticosteroids, and weight management, could lead to situations where conservative management slowed down or stopped disease progression so as to allow for development of effective interventions to reverse the joint damage and/or inhibit the need for arthroplasty.

**Key messages**

**Current data**

- Limitations due to variability in production and classification of PRP
- Low quality of published studies limits conclusions regarding PRP efficacy
- Diverse patient populations limit generalizability and characterization of subgroup responsiveness

**Future considerations**

- Standardization of PRP classification and reporting for future PRP studies
- Utilization of blinding, sham control arm, and randomization
- Reporting of patient (e.g., comorbidities, medications) to better characterize responsiveness to PRP

## Compliance with Ethical Standards

**Conflict of Interest**
Alison S. R. Kydd declares that she has no conflicts of interest. David A. Hart declares that he has no conflicts of interest.

**Human and Animal Rights and Informed Consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance


1. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1323–30. https://doi.org/10.1136/annrheumdis-2013-204763.
2. Hawker GA, Croxford R, Bierman AS, Harvey PJ, Ravi B, Stanaitis I, et al. All-cause mortality and serious cardiovascular events in people with hip and knee osteoarthritis: a population based cohort study. PLoS One. 2014;9(3):e91286. https://doi.org/10.1371/journal.pone.0091286.
3. March LCM, Lo C, Arden N, Gates L, Leyland K, Hawker G, King L. Osteoarthritis: a serious disease. Submitted to the U.S. Food and Drug Administration December 1, 2016. 2016. Available at https://www.oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa_serious_disease_121416_1.pdf.
4. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol. 2014;10(7):437–41. https://doi.org/10.1038/nrrheum.2014.44.
5. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthr Cartil. 2014;22(3):363–88. https://doi.org/10.1016/j.joca.2014.01.003.
6. Jevsevar DS. Treatment of osteoarthritis of the knee: evidence-based guideline. 2nd ed. American Academy of Orthopaedic Surgeons: Rosemont, IL, USA; 2013.
7. American Academy of Orthopaedic Surgeons. Management of osteoarthritis of the hip evidence-based clinical practice guideline. 2017. Available at https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-hip/oa-hip-cpg_6-11-19.pdf.
8. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthr Cartil. 2019. https://doi.org/10.1016/j.joca.2019.06.011.
9. Browne JA, Nho SJ, Goodman SB, Della Valle CJ. American Association of Hip and Knee Surgeons, Hip Society, and Knee Society position statement on biologics for advanced hip and knee arthritis. J Arthroplast. 2019;34(6):1051–2. https://doi.org/10.1016/j.arth.2019.03.068.
10. Deveza LA, Melo L, Yamato TP, Mills K, Ravi V, Hunter DJ. Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. Osteoarthr Cartil. 2017;25(12):1926–41. https://doi.org/10.1016/j.joca.2017.08.009.
11. Courties A, Berenbaum F, Sellam J. The phenotypic approach to osteoarthritis: a look at metabolic syndrome-associated osteoarthritis. Joint Bone Spine. 2018. https://doi.org/10.1016/j.jbspin.2018.12.005.
12. Berenbaum F. Deep phenotyping of osteoarthritis: a step forward. Ann Rheum Dis. 2019;78(1):3–5. https://doi.org/10.1136/annrheumdis-2018-213864.
13. Magnusson K, Turkiewicz A, Englund M. Nature vs nurture in knee osteoarthritis - the importance of age, sex and body mass index. Osteoarthr Cartil. 2019;27(4):586–92. https://doi.org/10.1016/j.joca.2018.12.018.
14. Magnusson K, Scurrah KJ, Orstavik RE, Nilsen TS, Furnes O, Hagen KB. Is the association between obesity and hip osteoarthritis surgery explained by familial confounding? Epidemiology. 2018;29(3):414–20. https://doi.org/10.1097/EDE.0000000000000806.
15. Felson DT. Epidemiology of hip and knee osteoarthritis. Epidemiol Rev. 1988;10:1–28. https://doi.org/10.1093/oxfordjournals.epirev.a036019.
16. Hussain SM, Cicuttini FM, Alyousef B, Wang Y. Female hormonal factors and osteoarthritis of the knee, hip and hand: a narrative review. Climacteric. 2018;21(2):132–9. https://doi.org/10.1080/13697137.2017.1421926.
17. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum. 2012;64(6):1697–707. https://doi.org/10.1002/art.34453.

18. Frank CB, Shrive NG, Boorman RS, Lo IK, Hart DA. New perspectives on bioengineering of joint tissues: joint adaptation creates a moving target for engineering replacement tissues. Ann Biomed Eng. 2004;32(3):458–65. https://doi.org/10.1023/b:abme.0000017548.85451.b7.
19. Collins KH, Herzog W, MacDonald GZ, Reimer RA, Rios JL, Smith IC, et al. Obesity, metabolic syndrome, and musculoskeletal disease: common inflammatory pathways suggest a central role for loss of muscle integrity. Front Physiol. 2018;9:112. https://doi.org/10.3389/fphys.2018.00112.
20. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthr Cartil. 2013;21(1):16–21. https://doi.org/10.1016/j.joca.2012.11.012.
21. Li MH, Xiao R, Li JB, Zhu Q. Regenerative approaches for cartilage repair in the treatment of osteoarthritis. Osteoarthr Cartil. 2017;25(10):1577–87. https://doi.org/10.1016/j.joca.2017.07.004.
22. Knutsen G, Drogset JO, Engebretsen L, Grontvedt T, Ludvigsen TC, Loken S, et al. A randomized multicenter trial comparing autologous chondrocyte implantation with microfracture: long-term follow-up at 14 to 15 years. J Bone Joint Surg Am. 2016;98(16):1332–9. https://doi.org/10.2106/jbjs.15.01208.
23. Shimomura K, Yasui Y, Koizumi K, Chijimatsu R, Hart DA, Yonetani Y, et al. First-in-human pilot study of implantation of a scaffold-free tissue-engineered construct generated from autologous synovial mesenchymal stem cells for repair of knee chondral lesions. Am J Sports Med. 2018;46(10):2384–93. https://doi.org/10.1177/0363546518781825.
24. Kim SH, Ha CW, Park YB, Nam E, Lee JE, Lee HJ. Intra-articular injection of mesenchymal stem cells for clinical outcomes and cartilage repair in osteoarthritis of the knee: a meta-analysis of randomized controlled trials. Arch Orthop Trauma Surg. 2019;139(7):971–80. https://doi.org/10.1007/s00402-019-03140-8.
25. Han Y, Huang H, Pan J, Lin J, Zeng L, Liang G, et al. Meta-analysis comparing platelet-rich plasma vs hyaluronic acid injection in patients with knee osteoarthritis. Pain Med. 2019. https://doi.org/10.1093/pm/pnz011.
26. Skou ST, Roos EM. Good Life with osteoArthritis in Denmark (GLA:D): evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. BMC Musculoskelet Disord. 2017;18(1):72. https://doi.org/10.1186/s12891-017-1439-y.
27. Davis AM, Kennedy D, Wong R, Robarts S, Skou ST, McGlasson R, et al. Cross-cultural adaptation and implementation of Good Life with osteoarthritis in Denmark (GLA:D): group education and exercise for hip and knee osteoarthritis is feasible in Canada. Osteoarthr Cartil. 2018;26(2):211–9. https://doi.org/10.1016/j.joca.2017.11.005.
28. Roos EM, Barton CJ, Davis AM, McGlasson R, Kemp JL, Crossley KM, et al. GLA:D to have a high-value option for patients with knee and hip arthritis across four continents: Good Life with osteoArthritis from Denmark. Br J Sports Med. 2018;52(24):1544–5. https://doi.org/10.1136/bjsports-2017-098904.
29. Marx RE. Platelet-rich plasma: growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 85(6):638–46. https://doi.org/10.1016/s1079-2104(98)90029-4.
30. Alves R, Grimalt R. A review of platelet-rich plasma: history, biology, mechanism of action, and classification. Skin Appendage Disord. 2018;4(1):18–24. https://doi.org/10.1159/000477353.
31. Moraes VY, Lenza M, Tamaoki MJ, Faloppa F, Belloti JC. Platelet-rich therapies for musculoskeletal soft tissue injuries. Cochrane Database Syst Rev. 2014;4:CD010071. https://doi.org/10.1002/14651858.CD010071.pub3.
32. O'Connell B, Wragg NM, Wilson SL. The use of PRP injections in the management of knee osteoarthritis. Cell Tissue Res. 2019;376(2):143–52. https://doi.org/10.1007/s00441-019-02996-x.
33. Vakharia RM, Roche MW, Alcerro JC, Lavernia CJ. The current status of cell-based therapies for primary knee osteoarthritis. Orthop Clin North Am. 2019;50(4):415–23. https://doi.org/10.1016/j.ocl.2019.06.001.
34. Canada H. Health Canada clarifies position on platelet rich plasma treatments. 2019. https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/70559a-eng.php.
35. Bottegoni C, Dei Giudici L, Salvemini S, Chiurazzi E, Bencivenga R, Gigante A. Homologous platelet-rich plasma for the treatment of knee osteoarthritis in selected elderly patients: an open-label, uncontrolled, pilot study. Ther Adv Musculoskelet Dis. 2016;8(2):35–41. https://doi.org/10.1177/1759720X16631188.
36. Gato-Calvo L, Magalhaes J, Ruiz-Romero C, Blanco FJ, Burguera EF. Platelet-rich plasma in osteoarthritis treatment: review of current evidence. Ther Adv Chronic Dis. 2019;10:2040622319825567. https://doi.org/10.1177/2040622319825567.
37. Dohan Ehrenfest DM, Andia I, Zumstein MA, Zhang C-Q, Pinto NR, Bielecki T. Classification of platelet concentrates (platelet-rich plasma-PRP, platelet-rich fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. Muscles Ligaments Tendons J. 2014;4(1):3–9.
38. Ziegler CG, Van Sloun R, Gonzalez S, Whitney KE, DePhillipo NN, Kennedy MI, et al. Characterization of growth factors, cytokines, and chemokines in bone marrow concentrate and platelet-rich plasma: a prospective analysis. Am J Sports Med. 2019;47(9):2174–87. https://doi.org/10.1177/0363546519832003.
39. Xu Z, Yin W, Zhang Y, Qi X, Chen Y, Xie X, et al. Comparative evaluation of leukocyte- and platelet-rich plasma and pure platelet-rich plasma for cartilage

regeneration. Sci Rep. 2017;7:43301. https://doi.org/10.1038/srep43301.

40. Oudelaar BW, Peerbooms JC, Huis in 't veld R, Vochteloo AJH. Concentrations of blood components in commercial platelet-rich plasma separation systems: a review of the literature. Am J Sports Med. 2019;47(2):479–87. https://doi.org/10.1177/0363546517746112.
41. Amable PR, Carias RB, Teixeira MV, da Cruz PI, Correa do Amaral RJ, Granjeiro JM, et al. Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. Stem Cell Res Ther. 2013;4(3):67. https://doi.org/10.1186/scrt218.
42. Fice MP, Miller JC, Christian R, Hannon CP, Smyth N, Murawski CD, et al. The role of platelet-rich plasma in cartilage pathology: an updated systematic review of the basic science evidence. Arthroscopy. 2019;35(3):961–76 e3. https://doi.org/10.1016/j.arthro.2018.10.125.
43. Khatab S, van Buul GM, Kops N, Bastiaansen-Jenniskens YM, Bos PK, Verhaar JA, et al. Intra-articular injections of platelet-rich plasma releasate reduce pain and synovial inflammation in a mouse model of osteoarthritis. Am J Sports Med. 2018;46(4):977–86. https://doi.org/10.1177/0363546517750635.
44. Kanwat H, Singh DM, Kumar CD, Alka B, Biman S, Aman H. The effect of intra-articular allogenic platelet rich plasma in Dunkin-Hartley guinea pig model of knee osteoarthritis. Muscles Ligaments Tendons J. 2017;7(3):426–34. https://doi.org/10.11138/mltj/2017.7.3.426.
45. Chouhan DK, Dhillon MS, Patel S, Bansal T, Bhatia A, Kanwat H. Multiple platelet-rich plasma injections versus single platelet-rich plasma injection in early osteoarthritis of the knee: an experimental study in a guinea pig model of early knee osteoarthritis. Am J Sports Med. 2019:363546519856605. https://doi.org/10.1177/0363546519856605.
46. Gato-Calvo L, Hermida-Gomez T, Ruiz Romero C, Burguera EF, Blanco FJ. Anti-inflammatory effects of novel standardized platelet rich plasma releasates on knee osteoarthritic chondrocytes and cartilage in vitro. Curr Pharm Biotechnol. 2019. https://doi.org/10.2174/1389201020666190619111118.
47. Zhang HF, Wang CG, Li H, Huang YT, Li ZJ. Intra-articular platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: a meta-analysis. Drug Des Dev Ther. 2018;12:445–53. https://doi.org/10.2147/DDDT.S156724.
48. Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. J Orthop Surg Res. 2017;12(1):16. https://doi.org/10.1186/s13018-017-0521-3.
49. Dai WL, Zhou AG, Zhang H, Zhang J. Efficacy of platelet-rich plasma in the treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. Arthroscopy. 2017;33(3):659–70 e1. https://doi.org/10.1016/j.arthro.2016.09.024.
50.•• Lin KY, Yang CC, Hsu CJ, Yeh ML, Renn JH. Intra-articular injection of platelet-rich plasma is superior to hyaluronic acid or saline solution in the treatment of mild to moderate knee osteoarthritis: a randomized, double-blind, triple-parallel, placebo-controlled clinical trial. Arthroscopy. 2019;35(1):106–17. https://doi.org/10.1016/j.arthro.2018.06.035 .

A randomized, double-blind trial comparing a single P-PRP intra-articular injection with a single hyaluronic acid injection or a normal saline sham control injection.

51. Newberry SJ, FitzGerald J, SooHoo NF, Booth M, Marks J, Motala A, et al. AHRQ comparative effectiveness reviews. Treatment of osteoarthritis of the knee: an update review. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017.
52. Saltzman BM, Leroux T, Meyer MA, Basques BA, Chahal J, Bach BR Jr, et al. The therapeutic effect of intra-articular normal saline injections for knee osteoarthritis: a meta-analysis of evidence level 1 studies. Am J Sports Med. 2017;45(11):2647–53. https://doi.org/10.1177/0363546516680607.
53. Paterson KL, Hunter DJ, Metcalf BR, Eyles J, Duong V, Kazsa J, et al. Efficacy of intra-articular injections of platelet-rich plasma as a symptom- and disease-modifying treatment for knee osteoarthritis - the RESTORE trial protocol. BMC Musculoskelet Disord. 2018;19(1):272. https://doi.org/10.1186/s12891-018-2205-5.
54.•• Di Martino A, Di Matteo B, Papio T, Tentoni F, Selleri F, Cenacchi A, et al. Platelet-rich plasma versus hyaluronic acid injections for the treatment of knee osteoarthritis: results at 5 years of a double-blind, randomized controlled trial. Am J Sports Med. 2019;47(2):347–54. https://doi.org/10.1177/0363546518814532.

A recent randomized, double-blind study comparing three weekly injections of either R-PRP or hyaluronic acid in knee OA.

55. Buendia-Lopez D, Medina-Quiros M, Fernandez-Villacanas Marin MA. Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial. J Orthop Traumatol. 2018;19(1):3. https://doi.org/10.1186/s10195-018-0501-3.
56. Lisi C, Perotti C, Scudeller L, Sammarchi L, Dametti F, Musella V, et al. Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial. Clin Rehabil. 2018;32(3):330–9. https://doi.org/10.1177/0269215517724193.
57. O'Donnell C, Migliore E, Grandi FC, Koltsov J, Lingampalli N, Cisar C, et al. Platelet-rich plasma (PRP) from older males with knee osteoarthritis depresses chondrocyte metabolism and upregulates inflammation. J Orthop Res. 2019. https://doi.org/10.1002/jor.24322.

58. Hirsch G, O'Neill TW, Kitas G, Sinha A, Klocke R. Accuracy of injection and short-term pain relief following intra-articular corticosteroid injection in knee osteoarthritis - an observational study. BMC Musculoskelet Disord. 2017;18(1):44. https://doi.org/10.1186/s12891-017-1401-z.
59. Briem K, Axe MJ, Snyder-Mackler L. Medial knee joint loading increases in those who respond to hyaluronan injection for medial knee osteoarthritis. J Orthop Res. 2009;27(11):1420–5. https://doi.org/10.1002/jor.20899.
60. Birchall D, Ismail AM, Peat G. Clinical outcomes from a physiotherapist-led intra-articular hyaluronic acid injection clinic. Musculoskeletal Care. 2008;6(3):135–49. https://doi.org/10.1002/msc.130.
61. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthr Cartil. 2004;12(5):389–99. https://doi.org/10.1016/j.joca.2004.02.001.
62. Dallari D, Stagni C, Rani N, Sabbioni G, Pelotti P, Torricelli P, et al. Ultrasound-guided injection of platelet-rich plasma and hyaluronic acid, separately and in combination, for hip osteoarthritis: a randomized controlled study. Am J Sports Med. 2016;44(3):664–71. https://doi.org/10.1177/0363546515620383.
63. Filardo G, Kon E, Pereira Ruiz MT, Vaccaro F, Guitaldi R, Di Martino A, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. Knee Surg Sports Traumatol Arthrosc. 2012;20(10):2082–91. https://doi.org/10.1007/s00167-011-1837-x.
64. Sanchez M, Fiz N, Azofra J, Usabiaga J, Aduriz Recalde E, Garcia Gutierrez A, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. Arthroscopy. 2012;28(8):1070–8. https://doi.org/10.1016/j.arthro.2012.05.011.
65. Su K, Bai Y, Wang J, Zhang H, Liu H, Ma S. Comparison of hyaluronic acid and PRP intra-articular injection with combined intra-articular and intraosseous PRP injections to treat patients with knee osteoarthritis. Clin Rheumatol. 2018;37(5):1341–50. https://doi.org/10.1007/s10067-018-3985-6.
66. Collins KH, Hart DA, Seerattan RA, Reimer RA, Herzog W. High-fat/high-sucrose diet-induced obesity results in joint-specific development of osteoarthritis-like degeneration in a rat model. Bone Joint Res. 2018;7(4):274–81. https://doi.org/10.1302/2046-3758.74.BJR-2017-0201.R2.

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