Platelet-rich plasma in the foot and ankle

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Abstract

Purpose of review Platelet-rich plasma has become an increasingly popular treatment option within the orthopedic community to biologically enhance and stimulate difficult-to-heal musculoskeletal tissues. This review evaluates the recent literature on platelet-rich plasma use in the treatment of foot and ankle pathologies.

Recent findings Recent literature has demonstrated platelet-rich plasma to have a possible benefit in the treatment of Achilles pathology, chronic plantar fasciitis, osteochondral lesions of the talus, ankle osteoarthritis, and diabetic foot ulcers. However, given the lack of standardization of platelet-rich plasma preparations and protocols and the predominance of low-quality studies, no definitive treatment indications exist.

Summary Platelet-rich plasma is a promising treatment option, but at present, there is only limited clinical evidence supporting its use in foot and ankle applications.

Keywords Platelet-rich plasma · PRP · Orthobiologics · Foot and ankle · Achilles

Introduction

Platelet-rich plasma (PRP) preparations were first described in the 1980s as plasma with a platelet count above that found normally in peripheral blood [1]. First used in the field of hematology, PRP use has expanded throughout the fields of dermatology, oral-maxillofacial surgery, plastic surgery, cardiac surgery, ophthalmology, urology, and gynecology [2]. However, PRP's predominant use has remained in the field of orthopedics as a treatment for both acute and chronic musculoskeletal pathologies.

Signaling molecules secreted by platelets include growth factors and cytokines which have downstream effects on local inflammatory reactions, recruitment and proliferation of stem cells, cell adhesion, and angiogenesis [3]. These molecules include platelet-derived growth factor, vascular endothelial

growth factor, fibroblast growth factor, insulin-like growth factors I and II, transforming growth factor beta, interleukin 8, and matrix metalloproteinases 2 and 9. By concentrating these molecules in PRP preparations and delivering them selectively to injured tissue, it is thought to enhance the natural healing response.

By nature of being an autologous blood concentrate, PRP has been categorized by the FDA as a minimally manipulated tissue and thus has been able to avoid the expensive premarket review and approval process required of other novel treatments [4]. This relatively light regulation, promising early in vitro and animal studies, and celebrity endorsements have fueled the current PRP boom [5–10]. Despite the increased use and popularity of PRP, the clinical efficacy of its use remains inconclusive. Clinicians continue to evaluate PRP's applications and effectiveness. This article provides a critical analysis of the recent literature on platelet-rich plasma treatment in orthopedic foot and ankle surgery.

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Platelet-rich plasma preparation

Significant variability exists regarding the formulation and production of PRP among commercial systems [11–13]. Variabilities include platelet concentration, leukocyte concentration, growth factor content, as well as differences

in separation and activation methods [14, 15]. Not only do these variabilities exist between subjects and systems, but they are also seen in single subjects using the same commercial system for production [16]. These inconsistencies have made it challenging to compare the available literature on PRP. To take a step toward optimizing the composition of PRP, recent efforts have attempted to determine the role of leukocyte concentration within PRP. Simplistically, leukocytes are the primary source of inflammatory cytokines and studies have shown an accumulation of these inflammatory mediators including IL-1 β , TNF- α , IL-6, and IL-8 in leukocyte-rich PRP [17–20]. Numerous studies evaluating the use of PRP in the treatment of tendinopathies have shown a benefit of leukocyte-reduced PRP over leukocyte-rich PRP due to the pro-inflammatory effects of leukocytes [17, 21–26]. In intra-articular applications, it has been suggested that leukocyte-reduced PRP is more efficacious and safer for the native cells [27–29]. Ultimately, further clinical and basic science research is necessary to determine the optimal formulation as well as the appropriate therapeutic protocol for each pathology.

Achilles tendon pathology

The Achilles tendon has a poor regenerative capability which makes treatment of Achilles tendon conditions difficult [30]. These conditions can either be acute Achilles tendon ruptures or chronic, degenerative Achilles tendinopathy.

Randomized control trials evaluating the effects of PRP injections for chronic midsubstance Achilles tendinopathy have been sparse and underpowered [30–34]. A summary of these studies is provided in Table 1. The pooled data from four randomized control trials was recently evaluated in a systematic review and meta-analysis by Zhang et al. [30, 32–34, 35]. A total of 170 patients with chronic Achilles tendinopathy enrolled in either a PRP injection plus eccentric strengthening group or a saline injection plus eccentric strengthening group [35]. These groups were evaluated at a final mean follow-up ranging from 3 to 12 months in the included studies. There was no significant difference between the PRP and saline groups regarding Victorian Institute of Sports Assessment-Achilles (VISA-A) scores, ultrasonographic evaluation of tendon thickness, or ultrasound color Doppler activity. Kearney

Table 1 PRP in the treatment of chronic Achilles tendinopathy—level I studies

Authors	Summary	Conclusion	Level of evidence
de Vos et al., JAMA, 2010 [33]	<ul style="list-style-type: none"> Stratified, block-randomized, double-blind, placebo-controlled trial at a single center comparing PRP vs saline injection with eccentric exercises for chronic noninsertional Achilles tendinopathy 	No significant difference between PRP and saline group at 24 months with regard to pain or activity.	Level I
de Jonge et al., Am J Sports Med, 2011 [30]	<ul style="list-style-type: none"> Randomized controlled trial evaluating clinical and ultrasonographic tissue effects of PRP versus saline injection with eccentric training program for patients with chronic noninsertional Achilles tendinopathy after 1 year 	No significant difference between VISA-A scores and ultrasonographic tendon evaluation of PRP injection versus saline injection at 1 year combined with an eccentric training program.	Level I
Krogh et al., Am J Sports Med, 2016 [32]	<ul style="list-style-type: none"> Randomized controlled trial evaluating VISA-A scores, pain at rest, pain while walking, pain with tendon squeeze, ultrasonographic tendon changes, and color Doppler activity after PRP versus saline injection in patients with chronic noninsertional Achilles tendinopathy at 3 months 	No significant difference between PRP and saline group at 3 months with regard to primary or majority of secondary outcomes. Tendon thickness was significantly increased in the PRP group at 3 months, but no further conclusions could be made owing to a large dropout rate after 3 months.	Level I
Boesen et al., Am J Sports Med, 2017 [34]	<ul style="list-style-type: none"> Randomized controlled trial evaluating VISA-A scores, VAS, ultrasonographic tendon thickness/vascularity, and muscle-function between high volume injection (HVI), PRP, and saline for the treatment of chronic noninsertional Achilles tendinopathy 	HVI and PRP showed significant benefit over placebo in all outcome measures at 6, 12, and 24 weeks of follow-up. HVI was significantly better than both PRP and placebo in the short-term (6 and 12 weeks).	Level I

et al. compared PRP injection with an eccentric loading program in 20 patients [31]. No significant difference was found between the groups during the first 6 months with outcome measures including VISA-A scores and EuroQol-5D. Guelfi et al. treated 83 cases of chronic noninsertional Achilles tendinopathy with a single PRP injection [36]. At a mean final follow-up of 50.1 months, the authors demonstrated significant improvements in VISA-A scores, Blazina score, and satisfaction index with no reported complications. Monto treated 30 patients with chronic noninsertional Achilles tendinopathy with a single PRP injection and followed American Orthopedic Foot and Ankle Society (AOFAS) scores at 0, 1, 2, 3, 6, 12, and 24 months posttreatment along with MRI and/or ultrasound [37]. AOFAS scores significantly improved at 3 months and remained significantly elevated at final follow-up. Pretreatment imaging abnormalities resolved in 27/29 patients at 6 months posttreatment. The above studies were all made up of relatively small sample sizes and future high-quality RCTs with larger sample sizes will be required to determine whether PRP injections are a viable or nonviable treatment option for chronic Achilles tendinopathy.

In contradistinction to chronic tendinopathy, acute Achilles tendon ruptures present a completely different set of problems for the orthopedic surgeon. Treatment options range from nonoperative treatment to minimally invasive or open surgery [38]. The *in vitro* benefits of PRP represent an attractive treatment adjunct to operative and nonoperative treatments as an adjunct for tendon and wound healing. High quality studies evaluating the use of PRP in acute Achilles tendon ruptures are extremely limited. Alsousou et al. evaluated 20 patients with an acute Achilles tendon rupture and randomized patients into a PRP treatment group or control group for both operative and nonoperative treatment arms [39]. Patients were followed for 1, 3, 6, 12, and 24 weeks with Achilles Tendon Rupture Score (ATRS), VISA-A, Foot and Ankle Outcome Score (FAOS), and functional ultrasound elastography (FUSE). ATRS, VISA-A, and FAOS scores were all significantly improved in the PRP group and FUSE scanning demonstrated larger, thicker tendons. De Carli et al. evaluated 30 patients surgically treated for Achilles tendon ruptures with and without adjunctive PRP injections [40]. MRI with contrast evaluation at 6 months postoperatively did show less signal enhancement in the PRP group compared to the control group which could indirectly represent improved tendon remodeling, but this did not result in appreciable clinical differences. There were no differences in VAS, FAOS, and VISA-A scores and no clinical difference in functional tests between the groups. Schepull et al. demonstrated that PRP had no significant effect on acute Achilles tendon repair in terms of elasticity and functional outcomes [41]. However, their results

were difficult to interpret given a large degree of variability between patients. Kaniki et al. retrospectively evaluated the use of PRP in nonoperative treatment of acute Achilles tendon ruptures as an adjunct to accelerated functional rehabilitation [42]. They found no benefit to the addition of PRP in terms of strength, ROM, calf circumference, or Leppilahti score. The above studies suggest no significant benefit to the addition of PRP to the operative or nonoperative treatment of acute Achilles tendon ruptures.

Plantar fasciitis

Plantar fasciitis is the most common cause of heel pain in adults [43]. The root cause being repetitive microtrauma resulting in inflammation and degeneration to the origin of the plantar fascia on the calcaneus. Treatment options range from orthotics, splints, stretching exercises, physical therapy, extracorporeal shock wave therapy (ESWT), medications, injectables, or surgical release [43]. Conservative measures remain the first line of treatment, but nonoperative management still fails in 10 to 15% of patients leading to chronic plantar fasciitis. Corticosteroids, autologous blood injection, and ESWT have been used with varying results and are not without risk including rupture of the plantar fascia after corticosteroid injections [44–46]. PRP is intriguing as an alternative treatment option to promote healing in the plantar fascia without significant risk.

Kumar Jain et al. compared single injections of PRP or corticosteroid in patients with chronic plantar fasciitis [47]. They found that both PRP and corticosteroid lead to significant improvements in VAS scores, modified Roles and Maudsley scores, Foot and Ankle Outcome Instrument core scale, and AOFAS ankle-hindfoot scale, but there was no significant difference between the two groups. Acosta-Olivo et al. demonstrated similar results showing that PRP had an efficacy equal to that of corticosteroids [48]. Aksahin et al. also showed significant improvement in VAS and modified Roles and Maudsley scores for both PRP and corticosteroid injections, but again, no significant difference between the groups. Recent studies comparing PRP versus corticosteroid injections with more long-term follow-up have demonstrated that PRP's effects may be longer lasting than corticosteroids [49–51]. Monto showed that PRP injections lead to improved AOFAS scores at 3 months and these improvements were maintained at 24 months postinjection [51]. These results were compared to corticosteroids which had an initial improvement in AOFAS scores at 3 months, but down trended back to baseline by 24 months. Jain et al. found similar results in their study looking at modified Roles and Maudsley scores,

VAS scores, and AOFAS scores [50]. PRP and corticosteroid had similar scores at 3 and 6 months, but at 12-month follow-up, PRP was significantly better. The results of the above studies and others were pooled in systematic review and meta-analysis by Singh et al. [52•]. The pooled data showed that PRP resulted in significant improvement over corticosteroid in VAS and AOFAS scores at 3 months, but no difference in pain or function scores at 1-, 6-, or 12-month follow-up. With the data available, it is uncertain whether the proposed limited benefit of PRP for the treatment of chronic plantar fasciitis is enough to offset the cost implications. Further well-designed, long-term, large-scale randomized controlled trials are needed to determine if PRP confers any benefit over corticosteroids.

Osteochondral lesions of the talus

With the advent of improved imaging technology, osteochondral lesions of the talus (OLT) are increasingly recognized as a source of ankle pain. Conservative management is often successful for small lesions, but for larger lesions or lesions that fail conservative treatment, surgical management is required. Surgical options fall broadly into reparative or reconstructive categories. Generally, these strategies have shown good success in short- to medium-term follow up, but valid concerns exist regarding long-term viability [53, 54]. New research is focused on improving the local biological milieu using PRP adjuncts in the setting of reparative or reconstructive procedures.

Guney et al. performed a randomized prospective study comparing patients treated with microfracture surgery alone versus microsurgery combined with PRP [55•]. At an average follow-up of 16.2 months, the authors found that both groups had significantly improved clinical outcomes as measured by AOFAS scores, Foot and Ankle Ability Measure (FAAM), and VAS, but the PRP group had superior outcomes to the microfracture-only group. Of note, the authors of this study excluded patients with a lesion diameter greater than 20 mm. Previous studies have shown that OCD lesions less than 15 mm in diameter were treated successfully with arthroscopic microfracture in the majority of patients [56, 57]. In a prospective randomized control trial, Gormeli et al. also compared AOFAS and VAS scores for OLT after microfracture surgery combined with PRP, hyaluronic acid (HA), and saline as a control group at a mean follow-up of 15.3 months [58]. While all groups exhibited significantly improved outcomes compared to baseline levels, PRP was found to produce significantly improved clinical scores compared to both HA and saline, with HA also being superior to the control group. Meidan et al. compared clinical and functional outcomes

following three intra-articular injections of either PRP or HA [59]. The authors showed that PRP treatment led to significantly better outcomes in pain and function compared to HA at 28 weeks. The evidence for PRP in the treatment of osteochondral lesions of the talus is promising, but further studies are needed to evaluate preparation, protocol, safety profile, and long-term results before a definitive conclusion can be made.

Ankle osteoarthritis

Osteoarthritis (OA) of the ankle is relatively uncommon in comparison to osteoarthritis of the hip or knee [60, 61]. Previous research has demonstrated clinical and functional improvements after intra-articular PRP injections in patients with knee OA [62–64]. Information regarding the use of PRP in ankle OA is limited to level IV case series. Repetto et al. evaluated 20 patients with symptomatic OA after four weekly PRP injections [65•]. At an average follow-up of 17.7 months, the authors found significant improvements in pain, function, and patient satisfaction. Fukawa et al. administered three PRP injections at two-week intervals to 20 patients with ankle OA [66]. The authors found significant improvement in pain and function up to 24 weeks after treatment. The maximal pain reduction did occur at 12 weeks after which pain began to trend toward baseline levels but remained significantly improved. Given the paucity of current evidence on PRP in ankle OA, no definitive conclusion can be made about its benefit at this time. The limited data does demonstrate some benefit in the short- to medium-term, but this needs to be compared to other injectables (corticosteroid, HA) in long-term, randomized controlled studies.

Osseous healing

The use of PRP for bone regeneration attempts to utilize the concentrated degranulation products of platelets to jumpstart the healing response at fracture and fusion sites around the foot and ankle. Many preclinical studies have shown PRP to be effective in enhancing osteogenesis [10, 67, 68]. However, the translation of the preclinical results to in vivo bone healing has yielded conflicting evidence. Wei et al. performed one of the only recent studies in the foot and ankle literature on PRP and osseous healing [69]. The authors prospectively compared the use of autograft versus allograft with and without PRP in surgically managed displaced intra-articular calcaneal fractures. At long-term follow-up, the AOFAS scores and radiographic parameters of the allograft with PRP group and autograft group were equivalent with both being superior to the

allograft alone group. Calcaneal fractures historically have a high union rate, but operative treatment also carries a high risk of wound complications. This study did not comment in enough detail to make any conclusions about wound healing with or without PRP. Bibbo et al. evaluated the use of autologous platelet concentrate (APC) in high-risk foot and ankle surgery patients undergoing elective procedures [70]. The authors defined high-risk patients as active smokers, diabetics with neuropathy, immunologically or nutritionally impaired, prior history of nonunion or delayed union, previous surgery at proposed operative site, and history of open treatment after high-energy trauma. Sixty-two high-risk patients were followed for 6 months with biweekly radiographs for assessment of radiographic union. Patients who received APC alone had a mean time to union of 40 days and patients who were treated with APC and autograft had a mean time to union of 45 days. The authors concluded that APC is a useful adjunct to promote osseous union in high-risk patients undergoing elective foot and ankle surgery. The hypothetical benefit of PRP in osseous healing is exciting, but many more studies are needed before any definitive conclusion can be made to support the use of PRP in human bone regeneration.

Wound healing

Recent studies have evaluated the role of PRP in wound healing [71–75]. Ahmed et al. compared PRP platelet gel applied twice weekly to daily antiseptic ointment dressing changes in the treatment of diabetic foot ulcers [74]. The platelet gel was prepared by centrifugation and activation at the patient's bedside with thrombin and calcium chloride. Once the platelet gel had formed a gelatinous disc, it was placed over the cleansed wound and nonabsorbable dressing applied. The authors found that PRP had significantly better healing rate and lower wound infection. Martinez-Zapata et al. performed a Cochrane Database systematic review and concluded that PRP may improve healing of diabetic foot ulcers but cautioned that this recommendation was based on low quality evidence [73]. Kane et al. evaluated the use of PRP in wound healing after total ankle arthroplasty [72]. They found no significant difference in wound healing complications between a group who underwent a nonaugmented closure and a group who underwent closure augmented with PRP. SanGiovanni et al. performed a prospective trial on patients undergoing a foot or ankle surgery randomized to wound closure with and without PRP [71]. There was no significant difference in postoperative complications between the groups including delayed wound healing and postoperative infection.

Conclusion

The use of PRP in Achilles pathology, chronic plantar fasciitis, osteochondral lesions of the talus, ankle osteoarthritis, and diabetic foot ulcers has shown some clinical benefit in the available studies. But given the abundance of conflicting and poor-quality evidence, no clear indications for the use of PRP currently exist. The lack of standardization in the PRP preparation and delivery method has contributed to the inconsistent results. Voices within the orthopedic community are calling for standardization of preparation protocols and reporting to allow study comparison and reproducibility [76]. Therapeutic protocols for timing of PRP administration and number of treatments must also be investigated and standardized. Differing pathologies will also likely require different PRP formulations and protocols to address specific biological needs.

However, PRP should not be abandoned as that would risk passing on a potentially effective treatment modality. Instead, further prospective randomized, controlled studies with standardized PRP formulations and protocols tailored to a specific pathology are needed to identify patient populations that can benefit from its application.

Compliance with ethical standards

Conflict of interest Both authors declare 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

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. 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>.
2. Andia E R-AJ, Martin I, Abate M. Current concepts and translational uses of platelet rich plasma biotechnology. *Biotechnology* 2015. <https://doi.org/10.5772/59954>.
3. Hall MP, Band PA, Meislin RJ, Jazrawi LM, Cardone DA. Platelet-rich plasma: current concepts and application in sports medicine. *J Am Acad Orthop Surg.* 2009;17(10):602–8.
4. Administration FaD. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products. Minimal manipulation and homologous use. In: Services USDoHaH, editor. Maryland: U.S. Department of Health and Human Services. p. 2017.

5. Mishra A, Tummala P, King A, Lee B, Kraus M, Tse V, et al. Buffered platelet-rich plasma enhances mesenchymal stem cell proliferation and chondrogenic differentiation. *Tissue Engineering Part C, Methods*. 2009;15(3):431–5. <https://doi.org/10.1089/ten.tec.2008.0534>.
6. Murray IR, LaPrade RF. Platelet-rich plasma: renewed scientific understanding must guide appropriate use. *Bone Joint Res*. 2016;5(3):92–4. <https://doi.org/10.1302/2046-3758.53.Bjr-2016-0005>.
7. Prins HJ, Rozemuller H, Vonk-Griffioen S, Verweij VG, Dhert WJ, Slaper-Cortenbach IC, et al. Bone-forming capacity of mesenchymal stromal cells when cultured in the presence of human platelet lysate as substitute for fetal bovine serum. *Tissue Eng A*. 2009;15(12):3741–51. <https://doi.org/10.1089/ten.TEA.2008.0666>.
8. Zaky SH, Ottonello A, Strada P, Cancedda R, Mastrogiacomo M. Platelet lysate favours in vitro expansion of human bone marrow stromal cells for bone and cartilage engineering. *J Tissue Eng Regen Med*. 2008;2(8):472–81. <https://doi.org/10.1002/term.119>.
9. Dolkart O, Chechik O, Zarfati Y, Brosh T, Alhajajra F, Maman E. A single dose of platelet-rich plasma improves the organization and strength of a surgically repaired rotator cuff tendon in rats. *Arch Orthop Trauma Surg*. 2014;134(9):1271–7. <https://doi.org/10.1007/s00402-014-2026-4>.
10. Iqbal J, Pepkowitz SH, Klapper E. Platelet-rich plasma for the replenishment of bone. *Curr Osteoporos Rep*. 2011;9(4):258–63. <https://doi.org/10.1007/s11914-011-0080-1>.
11. Castillo TN, Pouliot MA, Kim HJ, Dragoo JL. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. *Am J Sports Med*. 2011;39(2):266–71. <https://doi.org/10.1177/0363546510387517>.
12. Fitzpatrick J, Bulsara MK, McCrory PR, Richardson MD, Zheng MH. Analysis of platelet-rich plasma extraction: variations in platelet and blood components between 4 common commercial kits. *Orthop J Sports Med*. 2017;5(1):2325967116675272. <https://doi.org/10.1177/2325967116675272>.
13. Oh JH, Kim W, Park KU, Roh YH. Comparison of the cellular composition and cytokine-release kinetics of various platelet-rich plasma preparations. *Am J Sports Med*. 2015;43(12):3062–70. <https://doi.org/10.1177/0363546515608481>.
14. Weibrich G, Kleis WK, Streckbein P, Moergel M, Hitzler WE, Hafner G. Comparison of point-of-care methods for preparation of platelet concentrate (platelet-rich plasma). *Int J Oral Maxillofac Implants*. 2012;27(4):762–9.
15. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. *Am J Sports Med*. 2011;39(10):2135–40. <https://doi.org/10.1177/0363546511417792>.
16. Mazzocca AD, McCarthy MB, Chowaniec DM, Cote MP, Romeo AA, Bradley JP, et al. Platelet-rich plasma differs according to preparation method and human variability. *J Bone Joint Surg Am*. 2012;94(4):308–16. <https://doi.org/10.2106/jbjs.K.00430>.
17. McCarrel TM, Minas T, Fortier LA. Optimization of leukocyte concentration in platelet-rich plasma for the treatment of tendinopathy. *J Bone Joint Surg American volume*. 2012;94(19):e143(1–8). doi:<https://doi.org/10.2106/jbjs.L.00019>, e14e1438).
18. Aye MT, Palmer DS, Giulivi A, Hashemi S. Effect of filtration of platelet concentrates on the accumulation of cytokines and platelet release factors during storage. *Transfusion*. 1995;35(2):117–24.
19. Stack G, Snyder EL. Cytokine generation in stored platelet concentrates. *Transfusion*. 1994;34(1):20–5.
20. Muylle L, Joos M, Wouters E, De Bock R, Peetermans ME. Increased tumor necrosis factor alpha (TNF alpha), interleukin 1, and interleukin 6 (IL-6) levels in the plasma of stored platelet concentrates: relationship between TNF alpha and IL-6 levels and febrile transfusion reactions. *Transfusion*. 1993;33(3):195–9.
21. Hilber F, Loibl M, Lang S, Kerschbaum M, Brockhoff G, Angele P, et al. Leukocyte-reduced platelet-rich plasma increases proliferation of tenocytes treated with prednisolone: a cell cycle analysis. *Arch Orthop Trauma Surg*. 2017;137(10):1417–22. <https://doi.org/10.1007/s00402-017-2771-2>.
22. Wang SZ, Fan WM, Jia J, Ma LY, Yu JB, Wang C. Is exclusion of leukocytes from platelet-rich plasma (PRP) a better choice for early intervertebral disc regeneration? *Stem Cell Res Ther*. 2018;9(1):199. <https://doi.org/10.1186/s13287-018-0937-7>.
23. Zhang L, Chen S, Chang P, Bao N, Yang C, Ti Y, et al. Harmful effects of leukocyte-rich platelet-rich plasma on rabbit tendon stem cells in vitro. *Am J Sports Med*. 2016;44(8):1941–51. <https://doi.org/10.1177/0363546516644718>.
24. Yan R, Gu Y, Ran J, Hu Y, Zheng Z, Zeng M, et al. Intratendon delivery of leukocyte-poor platelet-rich plasma improves healing compared with leukocyte-rich platelet-rich plasma in a rabbit Achilles tendinopathy model. *Am J Sports Med*. 2017;45(8):1909–20. <https://doi.org/10.1177/0363546517694357>.
25. Boswell SG, Schnabel LV, Mohammed HO, Sundman EA, Minas T, Fortier LA. Increasing platelet concentrations in leukocyte-reduced platelet-rich plasma decrease collagen gene synthesis in tendons. *Am J Sports Med*. 2014;42(1):42–9. <https://doi.org/10.1177/0363546513507566>.
26. Cross JA, Cole BJ, Spatny KP, Sundman E, Romeo AA, Nicholson GP, et al. Leukocyte-reduced platelet-rich plasma normalizes matrix metabolism in torn human rotator cuff tendons. *Am J Sports Med*. 2015;43(12):2898–906. <https://doi.org/10.1177/0363546515608157>.
27. 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: official journal of the ESSKA*. 2012;20(10):2082–2091. doi:<https://doi.org/10.1007/s00167-011-1837-x>.
28. Braun HJ, Kim HJ, Chu CR, Dragoo JL. The effect of platelet-rich plasma formulations and blood products on human synoviocytes: implications for intra-articular injury and therapy. *Am J Sports Med*. 2014;42(5):1204–10. <https://doi.org/10.1177/0363546514525593>.
29. Riboh JC, Saltzman BM, Yanke AB, Fortier L, Cole BJ. Effect of leukocyte concentration on the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis. *Am J Sports Med*. 2016;44(3):792–800. <https://doi.org/10.1177/0363546515580787>.
30. de Jonge S, de Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, Verhaar JA, et al. One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. *Am J Sports Med*. 2011;39(8):1623–9. <https://doi.org/10.1177/0363546511404877>.
31. Kearney RS, Parsons N, Costa ML. Achilles tendinopathy management: a pilot randomised controlled trial comparing platelet-rich plasma injection with an eccentric loading programme. *Bone Joint Res*. 2013;2(10):227–32. <https://doi.org/10.1302/2046-3758.210.2000200>.
32. Krogh TP, Ellingsen T, Christensen R, Jensen P, Fredberg U. Ultrasound-guided injection therapy of Achilles tendinopathy with platelet-rich plasma or saline: a randomized, blinded, placebo-controlled trial. *Am J Sports Med*. 2016;44(8):1990–7. <https://doi.org/10.1177/0363546516647958>.
33. de Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, Verhaar JA, Weinans H, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. *JAMA*. 2010;303(2):144–9. <https://doi.org/10.1001/jama.2009.1986>.
34. Boesen AP, Hansen R, Boesen MI, Malliaras P, Langberg H. Effect of high-volume injection, platelet-rich plasma, and sham treatment in chronic midportion Achilles tendinopathy: a randomized double-

- blinded prospective study. *Am J Sports Med.* 2017;45(9):2034–43. <https://doi.org/10.1177/0363546517702862>.
35. Zhang YJ, Xu SZ, Gu PC, Du JY, CYZ, Zhang C, et al. Is platelet-rich plasma injection effective for chronic Achilles tendinopathy? A meta-analysis. *Clin Orthop Relat Res.* 2018. <https://doi.org/10.1007/s11999-0000000000000258> **Meta-analysis and systematic review of a total of 170 patients with chronic Achilles tendinopathy enrolled in either a PRP injection plus eccentric strengthening group or a saline injection plus eccentric strengthening group were evaluated. The authors found no significant difference between the PRP and saline groups regarding Victorian Institute of Sports Assessment-Achilles scores, ultrasonographic evaluation of tendon thickness, or ultrasound color Doppler activity.**
 36. Guelfi M, Pantalone A, Vanni D, Abate M, Guelfi MG, Salini V. Long-term beneficial effects of platelet-rich plasma for non-insertional Achilles tendinopathy. *Foot Ankle Surg.* 2015;21(3):178–81. <https://doi.org/10.1016/j.fas.2014.11.005>.
 37. Monto RR. Platelet rich plasma treatment for chronic Achilles tendinosis. *Foot Ankle Int.* 2012;33(5):379–85. <https://doi.org/10.3113/fai.2012.0379>.
 38. Wilkins R, Bisson LJ. Operative versus nonoperative management of acute Achilles tendon ruptures: a quantitative systematic review of randomized controlled trials. *Am J Sports Med.* 2012;40(9):2154–60. <https://doi.org/10.1177/0363546512453293>.
 39. Alsousou J, Handley R, Hulley P, Thompson M, McNally E, Harrison P, et al. Platelet rich plasma in accelerated achilles tendon regeneration: a randomized controlled trial. *Orthop Proc.* 2012;94-B(SUPP_XXXVI):6. https://doi.org/10.1302/1358-992x.94bsupp_xxxvi.Bors2011-006.
 40. De Carli A, Lanzetti RM, Ciompi A, Lupariello D, Vadala A, Argento G, et al. Can platelet-rich plasma have a role in Achilles tendon surgical repair? *Knee Surg Sports Traumatol Arthrosc.* 2016;24(7):2231–7. <https://doi.org/10.1007/s00167-015-3580-1> **Evaluated 30 patients surgically treated for Achilles tendon ruptures with and without adjunctive PRP injections. There were no differences in VAS, FAOS, and VISA-A scores and no clinical difference in functional tests between the groups. MRI with contrast evaluation at 6 months postoperatively did show less signal enhancement in the PRP group compared to the control group which could indirectly represent improved tendon remodeling, but this did not result in appreciable clinical differences.**
 41. Schepull T, Kvist J, Norrman H, Trinks M, Berlin G, Aspenberg P. Autologous platelets have no effect on the healing of human Achilles tendon ruptures: a randomized single-blind study. *Am J Sports Med.* 2011;39(1):38–47. <https://doi.org/10.1177/0363546510383515>.
 42. Kaniki N, Willits K, Mohtadi NG, Fung V, Bryant D. A retrospective comparative study with historical control to determine the effectiveness of platelet-rich plasma as part of nonoperative treatment of acute Achilles tendon rupture. *Arthroscopy.* 2014;30(9):1139–45. <https://doi.org/10.1016/j.arthro.2014.04.086>.
 43. Neufeld SK, Cerrato R. Plantar fasciitis: evaluation and treatment. *J Am Acad Orthop Surg.* 2008;16(6):338–46.
 44. David JA, Sankarapandian V, Christopher PR, Chatterjee A, Macaden AS. Injected corticosteroids for treating plantar heel pain in adults. *The Cochrane Database Syst Rev* 2017;6:Cd009348. <https://doi.org/10.1002/14651858.CD009348.pub2>.
 45. Genc H, Saracoglu M, Nacir B, Erdem HR, Kacar M. Long-term ultrasonographic follow-up of plantar fasciitis patients treated with steroid injection. *Joint, Bone, Spine : revue du rhumatisme.* 2005;72(1):61–5. <https://doi.org/10.1016/j.jbspin.2004.03.006>.
 46. Dorotka R, Sabeti M, Jimenez-Boj E, Goll A, Schubert S, Trieb K. Location modalities for focused extracorporeal shock wave application in the treatment of chronic plantar fasciitis. *Foot Ankle Int.* 2006;27(11):943–7. <https://doi.org/10.1177/107110070602701113>.
 47. Jain SK, Suprashant K, Kumar S, Yadav A, Kearns SR. Comparison of plantar fasciitis injected with platelet-rich plasma vs corticosteroids. *Foot Ankle Int.* 2018;39(7):780–6. <https://doi.org/10.1177/1071100718762406>.
 48. Acosta-Olivo C, Elizondo-Rodriguez J, Lopez-Cavazos R, Vilchez-Cavazos F, Simental-Mendia M, Mendoza-Lemus O. Plantar fasciitis-a comparison of treatment with intralesional steroids versus platelet-rich plasma a randomized, blinded study. *J Am Podiatr Med Assoc.* 2017;107(6):490–6. <https://doi.org/10.7547/15-125>.
 49. Vahdatpour B, Kianimehr L, Moradi A, Haghighat S. Beneficial effects of platelet-rich plasma on improvement of pain severity and physical disability in patients with plantar fasciitis: a randomized trial. *Adv Biomed Res.* 2016;5:179. <https://doi.org/10.4103/2277-9175.192731>.
 50. Jain K, Murphy PN, Clough TM. Platelet rich plasma versus corticosteroid injection for plantar fasciitis: a comparative study. *Foot (Edinburgh, Scotland).* 2015;25(4):235–7. <https://doi.org/10.1016/j.foot.2015.08.006>.
 51. Monto RR. Platelet-rich plasma efficacy versus corticosteroid injection treatment for chronic severe plantar fasciitis. *Foot Ankle Int.* 2014;35(4):313–8. <https://doi.org/10.1177/1071100713519778>.
 52. Singh P, Madanipour S, Bhamra JS, Gill I. A systematic review and meta-analysis of platelet-rich plasma versus corticosteroid injections for plantar fasciopathy. *Int Orthop.* 2017;41(6):1169–81. <https://doi.org/10.1007/s00264-017-3470-x> **The pooled data showed that PRP resulted in significant improvement over corticosteroid in VAS and AOFAS scores at 3 months, but no difference in pain or function scores at 1-, 6-, or 12-month follow-up. With the data available it is uncertain whether the proposed limited benefit of PRP for the treatment of chronic plantar fasciitis is enough to offset the cost implications.**
 53. Lee KB, Bai LB, Yoon TR, Jung ST, Seon JK. Second-look arthroscopic findings and clinical outcomes after microfracture for osteochondral lesions of the talus. *Am J Sports Med* 2009;37(Suppl 1):63s–70s. <https://doi.org/10.1177/0363546509348471>.
 54. Becher C, Driessen A, Hess T, Longo UG, Maffulli N, Thermann H. Microfracture for chondral defects of the talus: maintenance of early results at midterm follow-up. *Knee Surg Sports Traumatol Arthroscopy.* 2010;18(5):656–63. <https://doi.org/10.1007/s00167-009-1036-1>.
 55. Guney A, Akar M, Karaman I, Oner M, Guney B. Clinical outcomes of platelet rich plasma (PRP) as an adjunct to microfracture surgery in osteochondral lesions of the talus. *Knee Surg Sports Traumatol Arthrosc.* 2015;23(8):2384–9. <https://doi.org/10.1007/s00167-013-2784-5> **Randomized prospective study comparing patients treated with microfracture surgery alone versus microsurgery combined with PRP. At an average follow-up of 16.2 months, the authors found that both groups had significantly improved clinical outcomes, but the PRP group had superior outcomes to the microfracture-only group. Of note study only involved OLT's less than 20mm in diameter.**
 56. Chuckpaiwong B, Berkson EM, Theodore GH. Microfracture for osteochondral lesions of the ankle: outcome analysis and outcome predictors of 105 cases. *Arthroscopy.* 2008;24(1):106–12. <https://doi.org/10.1016/j.arthro.2007.07.022>.
 57. Choi WJ, Park KK, Kim BS, Lee JW. Osteochondral lesion of the talus: is there a critical defect size for poor outcome? *Am J Sports Med.* 2009;37(10):1974–80. <https://doi.org/10.1177/0363546509335765>.
 58. Gormeli G, Karakaplan M, Gormeli CA, Sarikaya B, Elmali N, Ersoy Y. Clinical effects of platelet-rich plasma and hyaluronic acid as an additional therapy for talar osteochondral lesions treated with

- microfracture surgery: a prospective randomized clinical trial. *Foot Ankle Int.* 2015;36(8):891–900. <https://doi.org/10.1177/1071100715578435>.
59. Mei-Dan O, Carmont MR, Laver L, Mann G, Maffulli N, Nyska M. Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus. *Am J Sports Med.* 2012;40(3):534–41. <https://doi.org/10.1177/0363546511431238>.
 60. Muehleman C, Bareither D, Huch K, Cole AA, Kuettner KE. Prevalence of degenerative morphological changes in the joints of the lower extremity. *Osteoarthr Cartil.* 1997;5(1):23–37.
 61. Cushnaghan J, Dieppe P. Study of 500 patients with limb joint osteoarthritis. I. Analysis by age, sex, and distribution of symptomatic joint sites. *Ann Rheum Dis.* 1991;50(1):8–13.
 62. 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>.
 63. Ornetti P, Nourissat G, Berenbaum F, Sellam J, Richette P, Chevalier X. Does platelet-rich plasma have a role in the treatment of osteoarthritis? *Joint Bone Spine : revue du rhumatisme.* 2016;83(1):31–6. <https://doi.org/10.1016/j.jbspin.2015.05.002>.
 64. Kon E, Buda R, Filardo G, Di Martino A, Timoncini A, Cenacchi A et al. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. *Knee Surg Sports Traumatol Arthrosc.* 2010;18(4):472–479. <https://doi.org/10.1007/s00167-009-0940-8>.
 65. • Repetto I, Biti B, Cerruti P, Trentini R, Felli L. Conservative treatment of ankle osteoarthritis: can platelet-rich plasma effectively postpone surgery? *J Foot Ankle Surg.* 2017;56(2):362–5. <https://doi.org/10.1053/j.jfas.2016.11.015> **Evaluated 20 patients with symptomatic ankle OA after four weekly PRP injections. At an average follow-up of 17.7 months, the authors found significant improvements in pain, function, and patient satisfaction.**
 66. Fukawa T, Yamaguchi S, Akatsu Y, Yamamoto Y, Akagi R, Sasho T. Safety and efficacy of intra-articular injection of platelet-rich plasma in patients with ankle osteoarthritis. *Foot Ankle Int.* 2017;38(6):596–604. <https://doi.org/10.1177/1071100717700377>.
 67. Celotti F, Colciago A, Negri-Cesi P, Pravettoni A, Zaninetti R, Sacchi MC. Effect of platelet-rich plasma on migration and proliferation of SaOS-2 osteoblasts: role of platelet-derived growth factor and transforming growth factor-beta. *Wound Repair Regen.* 2006;14(2):195–202. <https://doi.org/10.1111/j.1743-6109.2006.00110.x>.
 68. Casati L, Celotti F, Negri-Cesi P, Sacchi MC, Castano P, Colciago A. Platelet derived growth factor (PDGF) contained in platelet rich plasma (PRP) stimulates migration of osteoblasts by reorganizing actin cytoskeleton. *Cell Adhes Migr.* 2014;8(6):595–602. <https://doi.org/10.4161/19336918.2014.972785>.
 69. Wei LC, Lei GH, Sheng PY, Gao SG, Xu M, Jiang W, et al. Efficacy of platelet-rich plasma combined with allograft bone in the management of displaced intra-articular calcaneal fractures: a prospective cohort study. *J Orthop Res.* 2012;30(10):1570–6. <https://doi.org/10.1002/jor.22118>.
 70. Bibbo C, Bono CM, Lin SS. Union rates using autologous platelet concentrate alone and with bone graft in high-risk foot and ankle surgery patients. *J Surg Orthop Adv.* 2005;14(1):17–22.
 71. SanGiovanni TP, Kiezbak GM. Prospective randomized evaluation of intraoperative application of autologous platelet-rich plasma on surgical site infection or delayed wound healing. *Foot Ankle Int.* 2016;37(5):470–7. <https://doi.org/10.1177/1071100715623994>.
 72. Kane JM, Costanzo JA, Raikin SM. The efficacy of platelet-rich plasma for incision healing after total ankle replacement using the agility total ankle replacement system. *Foot Ankle Int.* 2016;37(4):373–7. <https://doi.org/10.1177/1071100715619681>.
 73. Martinez-Zapata MJ, Marti-Carvajal AJ, Sola I, Exposito JA, Bolibar I, Rodriguez L et al. Autologous platelet-rich plasma for treating chronic wounds. *The Cochrane Database Syst Rev* 2016(5):Cd006899. <https://doi.org/10.1002/14651858.CD006899.pub3>.
 74. Ahmed M, Reffat SA, Hassan A, Eskander F. Platelet-rich plasma for the treatment of clean diabetic foot ulcers. *Ann Vasc Surg.* 2017;38:206–11. <https://doi.org/10.1016/j.avsg.2016.04.023>.
 75. Babaei V, Afradi H, Gohardani HZ, Nasseri F, Azarafza M, Teimourian S. Management of chronic diabetic foot ulcers using platelet-rich plasma. *J Wound Care.* 2017;26(12):784–7. <https://doi.org/10.12968/jowc.2017.26.12.784>.
 76. Chahla J, Cinque ME, Piuze NS, Mannava S, Geeslin AG, Murray IR, et al. A call for standardization in platelet-rich plasma preparation protocols and composition reporting: a systematic review of the clinical orthopaedic literature. *J Bone Joint Surg.* 2017;99(20):1769–79. <https://doi.org/10.2106/jbjs.16.01374>.