Conservative Treatment of Ankle Osteoarthritis: Can Platelet-Rich Plasma Effectively Postpone Surgery?

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ABSTRACT

Osteoarthritis is the most common and disabling of the orthopedic diseases. Currently, the conservative treatment of osteoarthritis is limited to symptomatic treatment, whose goal is to improve function and pain control. Ankle osteoarthritis is relatively uncommon, in contrast to osteoarthritis of the hip and knee, and the therapeutic options (both pharmacologic and surgical) are limited, with surgery providing poorer and less predictable results. The effectiveness of platelet-rich plasma injections for osteoarthritis is still controversial, especially so for ankle arthritis, owing to the lack of evidence in the present data. We retrospectively evaluated the mid- to long-term clinical results (mean follow-up of 17.7 months) for platelet-rich plasma injections in 20 patients (20 ankles) with ankle osteoarthritis. We evaluated the presence of pain using the visual analog scale, function using the Foot and Ankle Disability Index, and subjective satisfaction. The pre- and post-treatment scores, obtained from the clinical records and from telephone interviews during the follow-up period, were compared using the Student t test. We found a strong positive effect for 4 platelet-rich plasma injections (injected once a week) on pain ($p = .0001$) and function ($p = .001$), with 80% of patients very satisfied and satisfied, and only 2 patients (10%) required surgery because of early treatment failure. These results suggest that the use of platelet-rich plasma injection is a valid and safe alternative to postpone the need for surgery.

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Symptomatic ankle osteoarthritis (OA) is a relatively uncommon condition, affecting 1% to 4% of the population (1–3), that leads to increasing pain with weightbearing and an impaired level of work and sports activity (4). First-line treatments for such a disabling condition consist of antiinflammatory drugs or pain killers, physical therapy, and intra-articular injections (corticosteroid and hyaluronic acid) (5).

Intra-articular platelet-rich plasma (PRP) injections are a newer solution that could be effective in pain reduction and improving joint function. Most of the published data regarding PRP have focused on its effectiveness in knee early-stage chondropathy and arthritis and degenerative tendinopathy (6,7). The role of PRP injections for ankle OA remains controversial, and only 2 studies (8,9) have been reported. The use of PRP injection in orthopedic pathologic entities has been debated owing to the poor level of evidence and reliability of many of the existing studies. Moreover, the most representative target of PRP has been early-stage chondropathy, although some recent studies on its effectiveness for medium-advanced knee OA were recently published, suggesting a widening of indications (10–14). PRP has been proved to be effective in improving pain, function, and quality of life in knee OA; however, to the best of our knowledge, no study has verified the same outcomes for ankle OA.

The aim of the present study was to assess the clinical effectiveness and feasibility of PRP injections in post-traumatic medium to advanced ankle OA to improve symptoms and delay the necessity for invasive surgical procedures.

Case Series Report

We retrospectively evaluated 20 patients with symptomatic ankle OA treated with intra-articular PRP injections at our institution from January 2013 to January 2014. The inclusion criteria were painful ankle OA, failure of almost 6 months of previous treatment, the presence of instrumental signs of medium to advanced OA graded using the

Kellgren-Lawrence classification (grade 3 to 4), age <65 years, and almost 6 months between previous therapies (both conservative and surgical, except for antiinflammatory drugs and pain killers) and the first injection of PRP. The exclusion criteria were treatment with antiinflammatory drugs or pain killers, nonambulation, pregnancy or lactation, concomitant systemic disease, open wounds or skin ulcers, the use of anticoagulants, and/or a prolonged bleeding time.

We performed a clinical examination, and each patient underwent a systematic evaluation of pain using a visual analog scale (VAS) and of function using the Foot and Ankle Disability Index (FADI). The results of the VAS and FADI were recorded in a hospital database. All the patients underwent weightbearing radiographs (anteroposterior, lateral) to assess the grade of articular degeneration. Only patients with moderate or advanced OA were included in the present study (Kellgren-Lawrence stage 3 to 4) (15). From their medical history, all the patients had reported previous ankle injuries (fracture or sprains) that had been first treated by physical therapy and hyaluronic acid injections, and 4 patients had undergone previous arthroscopic debridement without long-term benefits.

A blood sample of 450 ml was taken from the patients and examined by the transfusion medicine department. The blood underwent a standardized protocol of preparation, which consisted of 3 centrifugations (Hettich Zentrifugen®; Hettich Lab Technology, Tuttlingen, Germany): the first at 3550 rpm for 12 minutes, the second at 1100 rpm for 10 minutes, and the last at 2600 rpm for 20 minutes. The final product was then filtered and frozen ($-80°C$) in 4 samples for cryopreservation.

The platelet concentration in this type of PRP is 2 to 3 times the blood platelet count (range 250,000 to 900,000, mean 600,000 cells/μL), which is considered to be moderately elevated. Moderately elevated platelet concentrations seem to induce optimal biologic benefit, with lower platelet concentrations leading to suboptimal effects and higher platelet concentrations to inhibitory effects (16–19). The leukocytes were filtered during the preparation, and their concentration in the final product was low (<1000 cells/μL).

Our institute protocol provides 4 injections of 3 mL of PRP once a week for each patient. The injection process is performed under strictly sterile conditions using an anteromedial approach to the ankle joint by the same physician (R.T.). No local anesthetic was used to prevent a possible negative interaction. Immediately after injection, the ankle joint was moved passively throughout its full range of motion to disseminate the fluid throughout the joint. The patients were advised to rest, apply ice, and avoid unnecessary walking for 24 hours. Acetaminophen (paracetamol) was recommended as an analgesic, if needed; however, the patients were instructed to abstain from taking nonsteroidal antiinflammatory drugs during treatment and for 2 weeks after the last injection to prevent possible negative interactions with the mechanism action of PRP. The patients were also instructed to stop sports activity or heavy physical work during the treatment time.

All the patients included in the present study were interviewed by telephone. Also, the VAS and FADI were administered to retrospectively assess the effectiveness of the treatment at medium- to long-term follow-up in terms of pain relief, level of activity/self-reported function, and subjective satisfaction.

The VAS indicates the subjective feeling of pain, with 0 indicating no pain and 10 indicating the worst pain the patient has ever experienced (20). The FADI is one of the most accredited evaluative instruments to quantify functional disabilities (21,22). It was first described in 1999 by Martin and Irrgang (23). It is a 26-item questionnaire that contains 4 pain-related questions and 22 activity-related questions. The 22 activity-related questions are scored on a 5-point scale from 0 (unable to do) to 4 (no difficulty at all). The 4 pain-related items of the FADI are scored from 0 (unbearable) to 4 (none). The FADI has a total point value of 104 points and is calculated as percentages, with 100% representing no dysfunction. The patient self-reported subjective satisfaction was recorded as very satisfied, satisfied, or partially satisfied or unsatisfied.

The pre- and post-treatment scores were compared using the Student *t* test. A *p* value < .01 was considered statistically significant.

Results

The demographic characteristics of the series and subjective satisfaction are listed in Table 1. The mean patient age was 57.5 (range 41 to 65) years, with a male prevalence (60%). The mean follow-up period was 17.7 ± 6.4 (range 12 to 30) months, with an average period between symptoms beginning and treatment of 26 (range 12 to 60) months. The FADI and VAS scores before treatment and at the follow-up point are listed in Table 2.

The Student *t* test demonstrated that our protocol for PRP injection in ankle OA is effective in improving function (FADI) and pain control (VAS) with high statistical significance ($p = .001$ and $p = .0001$, respectively; Figs. 1 and 2). Also, 18 of the 20 patients (80%) were satisfied and very satisfied and were able to return to their previous level of activity. The remaining 2 patients (10%) experienced only partial or temporary benefits (Table 3). No adverse effects or complications subsequent to the PRP injections were recorded. No statistically significant difference was found in the scores of the FADI and VAS between the subgroup of patients who had undergone arthroscopic debridement before PRP injection (4 patients) and the 16 patients who had not ($p = .6632$ and $p = .2663$, respectively; Student *t* test).

Four patients reported poor results from the treatment, and the mean interval between the end of the treatment and the relapse of symptoms was 3.75 (range 2 to 6) months. Of these patients, 2 underwent intra-articular injection of autologous adipose-derived stem cells (Lipogems International SpA, Milan, Italy), 1 underwent arthroscopy (debridement and removal of an anterior osteophyte),

Table 1
Baseline data (N = 20 ankles in 20 patients)

Variable	Value
Age (yr)	
Mean ± SD	57.5 ± 7.9
Range	41 to 65
Gender	
Male	12 (60)
Female	8 (40)
Follow-up (mo)	
Mean ± SD	17.7 ± 6.4
Range	12 to 30
Interval between symptoms to PRP injection (mo)	
Mean ± SD	26 ± 14.7
Range	12 to 60
Kellgren-Lawrence grade	
3	11 (55)
4	9 (45)

Abbreviations: PRP, platelet-rich plasma; SD, standard deviation.
Data presented as n (%) or mean ± SD and range.

Table 2
Pre- and post-injection outcome scores of study population (N = 20 ankles in 20 patients)

	Average	SD	Range
FADI score			
Before treatment	59.22	13.60	37.5 to 74
After treatment	80.21	17.28	46.2 to 100
VAS score			
Before treatment	7.8	0.5	7 to 9
After treatment	2.6	2.2	0 to 7

Abbreviations: FADI, Foot Ankle Disability Index; SD, standard deviation; VAS, visual analog scale.
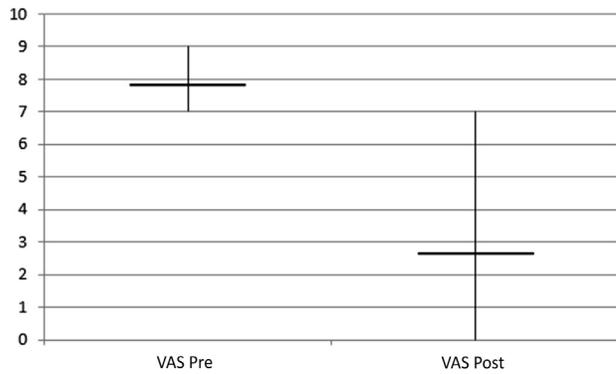
Fig. 1. Graph showing pre- and post-treatment visual analog scale (VAS) pain scores ($p = .0001$) (N = 20).

and 1 underwent ankle fusion. All 4 patients experienced good short-term benefits.

Discussion

OA is the most common and disabling of the orthopedic diseases. It represents an important economic burden owing to its high prevalence in the general population and its clinical presentation, which is characterized by worsening chronic pain and progressive disability (24). The conservative treatment of OA has been is limited to symptomatic treatment, with the goal of improving function and controlling pain. No drugs are capable of inducing clinically relevant chondroprotective effects (25).

OA of the tibiotalar joint is relatively uncommon compared with OA of the hip and knee joints. OA of the tibiotalar joint progresses from early damage to diffuse and severe degeneration and deformity of the joint (1–3,26,27). The leading causes include trauma, ischemia, abnormal ossification, and genetic predisposition (28,29). Although trauma is probably the most likely cause of injury and degenerative involution of the ankle (70% of reported cases), repetitive microtrauma could also be a contributing factor (30). Despite the high prevalence of ankle trauma and related chondral lesions (31), the rate of symptomatic and disabling OA is lower than that of the hip and knee, owing to the different biologic and biomechanical characteristic of the ankle's cartilage and subchondral bone (32,33). Cartilage lesions in many cases will heal spontaneously and remain asymptomatic, or they can develop into subchondral cysts or detach,
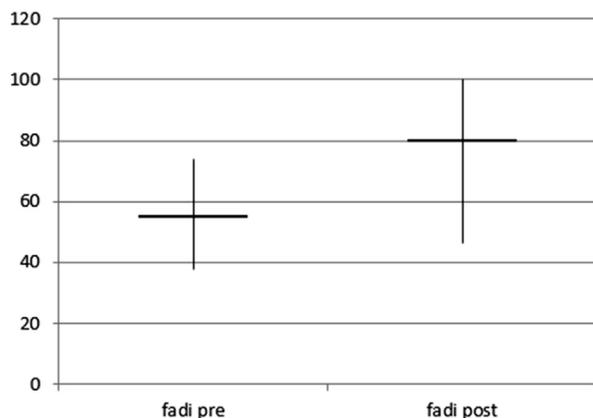
forming intra-articular loose bodies that result in chronic symptoms of deep joint pain that become worse with weightbearing and exercise (29,34,35). Catching, stiffness, and joint swelling have also been reported.

The goals of treatment are to improve joint function, reduce pain, and prevent additional joint degeneration. The nonoperative treatment options are limited (36) and tend to be reserved for grade 1 and 2 chondropathy. The conservative treatment options include rest, immobilization, limitation of weightbearing, physical therapy, and intra-articular injections (steroid or hyaluronic acid).

Surgery has been recommended after almost 6 months of unsuccessful nonoperative treatment (35,36). The surgical procedures include curettage and microfracture, retrograde and antegrade drilling, osteochondral fragment/loose body removal, large fragment fixation, abrasion arthroplasty, bone or cartilage transplantation and, in the latest stages, total arthroplasty and arthrodesis (27,34,36–40).

In recent years, the musculoskeletal benefits of PRP have been the focus of considerable interest, most notably in sports medicine and orthopedics (41–43). Most of the published data on PRP have focused on its effectiveness to treat degenerative tendinopathy or early-stage knee chondropathy and arthritis, with its use enlarging to the latest pathologic stage (6,7,12–14). Regarding the use of PRP for ankle OA, we found only 2 reports (8,9) that attested to the effectiveness of intra-articular injection of PRP in the treatment of the painful ankle. However, they considered only early-stage osteochondral lesions and ankle chondropathy. The published data are controversial on this topic owing to the lack of evidence and reliability of many of the existing studies.

PRP has been proved to reduce pain and improve articular function and the quality of life in knee OA, resulting in a widening of indications (10–14). However, to the best of our knowledge, no study has verified the same effects for PRP injection to treat ankle OA.

In the present retrospective study, we found a positive effect for 4 PRP injections (once each week) on pain reduction ($p = .0001$) and function improvement ($p = .001$) at the medium-term follow-up point (mean 17.7 months), adding promising results to the available evidence. It is important to note that all the patients involved in the present study had just been treated with hyaluronic acid and 4 had previously undergone arthroscopic debridement without significant long-term benefits. The patients were considered eligible for the study if the previous treatment had been concluded almost 6 months before the PRP injections began to minimize bias. No additional benefit from the treatment was seen in the patients who had undergone arthroscopic debridement before PRP injection, although the finding is limited by the small number of the patients (n = 4).

Our findings seem to confirm the clinical benefit of PRP injections for ankle OA, as previously described by Mei-Dan et al (8) for early osteochondral lesions of the talus and Vannini et al (43) for early-stage ankle chondropathy. No complications were recorded, and only 2 patients underwent surgery because of short-term treatment failure (and only 1 patient underwent ankle fusion), confirming PRP as a reliable and safe alternative to treat ankle OA to delay invasive surgical procedures as prosthesis or ankle fusion, especially for younger patients.

Fig. 2. Graph showing pre- and post-treatment Foot Ankle Disability Index (fadi) function scores ($p = .001$) (N = 20).

Table 3
Level of self-reported subjective satisfaction after treatment (N = 20 ankles in 20 patients)

Subjective Satisfaction	Patients (n)
Less satisfied	4 (20)
Satisfied	9 (45)
Very satisfied	7 (35)

Data in parentheses are percentages.

The present study had several limitations owing to the small number of patients and the retrospective design. Nevertheless, the present study is the first study to evaluate the effectiveness of PRP in the symptomatic treatment of recalcitrant and medium- to advanced-stage ankle OA. Further randomized controlled prospective trials are needed to strengthen the level of evidence.

References

1. 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 50:8–13, 1991.
2. Huch K, Kuettner KE, Dieppe P. Osteoarthritis in ankle and knee joints. Semin Arthritis Rheum 26:667–674, 1997.
3. Muehleman C, Bareither D, Huch K, Cole AA, Kuettner KE. Prevalence of degenerative morphological changes in the joints of the lower extremity. Osteoarthritis Cartilage 5:23–37, 1997.
4. Glazebrook M, Daniels T, Younger A, Foote CJ, Penner M, Wing K, Lau J, Leighton R, Dunbar M. Comparison of health-related quality of life between patients with end-stage ankle and hip arthrosis. J Bone Joint Surg Am 90:499–505, 2008.
5. Witteveen AGH, Hofstad CJ, Kerkhoffs GMMJ. Hyaluronic acid and other conservative treatment options for osteoarthritis of the ankle (review). Cochrane Database Syst Rev:CD010643, 2015.
6. Vannini F, Di Matteo B, Filardo G, Kon E, Marcacci M, Giannini S. Platelet-rich plasma for foot and ankle pathologies: a systematic review. Foot Ankle Surg 20:2–9, 2014.
7. Soomekh DJ. Current concepts for the use of platelet-rich plasma in the foot and ankle. Clin Podiatr Med Surg 28:155–170, 2011.
8. 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 40:534–541, 2012.
9. Angthong C, Khadsongkram A, Angthong W. Outcomes and quality of life after platelet-rich plasma therapy in patients with recalcitrant hindfoot and ankle diseases: a preliminary report of 12 patients. J Foot Ankle Surg 52:475–480, 2013.
10. Kon E, Buda R, Filardo G, Timoncini A, Di Martino A, Cenacchi A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surg Sports Traumatol Arthrosc 18:472–479, 2010.
11. Kon E, Mandelbaum B, Buda R, Delcogliano M, Timoncini A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy 27:1490–1501, 2011.
12. Ornetti P, Nourissat G, Berenbaumd F, Sellamd J, Richettef P, Chevalierg X. Does platelet-rich plasma have a role in the treatment of osteoarthritis? Joint Bone Spine 83:31–36, 2016.
13. Laudy AB, Bakker EW, Rekers M, Moen MH. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. Br J Sports Med 49:657–672, 2015.
14. Campbell KA, Saltzman BM, Mascarenhas R, Khair MM, Verma NN, Bach BR Jr, Cole BJ. Does intra-articular platelet-rich plasma injection provide clinically superior outcomes compared with other therapies in the treatment of knee osteoarthritis? A systematic review of overlapping meta-analyses. Arthroscopy 31:2213–2221, 2015.
15. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 16:494–502, 1957.
16. Weibrich G, Hansen T, Kleis W, Buch R, Hitzler WE. Effect of platelet concentration in platelet-rich plasma on peri-implant bone regeneration. Bone 34:665–671, 2004.
17. Graziani F, Ivanovski S, Cei S, Ducci F, Tonetti M, Gabriele M. The in vitro effect of different PRP concentrations on osteoblasts and fibroblasts. Clin Oral Implants Res 17:212–219, 2006.
18. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. Curr Rev Musculoskelet Med 1:165–174, 2008.
19. Smyth NA, Murawski CD, Fortier LA, Cole BJ, Kennedy JG. Platelet-rich plasma in the pathologic processes of cartilage: review of basic science evidence. Arthroscopy 29:1399–1409, 2013.
20. Joyce CR, Zutshi DW, Hrubes V, Mason RM. Comparison of fixed interval and visual analogue scales for rating chronic pain. Eur J Clin Pharmacol 8:415–420, 1975.
21. Hale SA, Hertel J. Reliability and sensitivity of the Foot and Ankle Disability Index in subjects with chronic ankle instability. J Athletic Training 40:35–40, 2005.
22. Eechaute C, Vaes P, Van Aerschot L, Asman S, Duquet W. The clinimetric qualities of patient-assessed instruments for measuring chronic ankle instability: a systematic review. BMC Musculoskelet Disord 8:6, 2007.
23. Martin RL, Irrgang JJ. A survey of self-reported outcome instruments for the foot and ankle. J Orthop Sports Phys Ther 37:72–84, 2007.
24. Guillemin F, Rat A-C, Roux CH, Fautrel B, Mazieres B, Chevalier X. The KHOALA cohort of knee and hip osteoarthritis in France. Joint Bone Spine 79:597–603, 2012.
25. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis. Osteoarthritis Cartilage 18:476–499, 2010.
26. Van Dijk CN, Reilingh ML, Zengerink M, van Bergen CJ. Osteochondral defects in the ankle: why painful? Knee Surg Sports Traumatol Arthrosc 18:570–580, 2010.
27. Raikin SM, Rasouli MR, Espandar R, Maltenfort MG. Trends in treatment of advanced ankle arthropathy by total ankle replacement or ankle fusion. Foot Ankle Int 35:216–224, 2014.
28. Formica M, Santolini F, Alessio-Mazzola M, Repetto I, Andretta A, Stella M. Closed medial malleolar multifragment fracture with a posterior tibialis tendon rupture: a case report and review of the literature. J Foot Ankle Surg 55:832–837, 2016.
29. Hixon AL, Gibbs LM. Osteochondritis dissecans: a diagnosis not to miss. Am Fam Physician 61:151–158, 2000.
30. Zengerink M, Struijs PA, Tol JL, van Dijk CN. Treatment of osteochondral lesions of the talus: a systematic review. Knee Surg Sports Traumatol Arthrosc 18:238–246, 2010.
31. Smyth NA, Murawski CD, Haleem AM, Hannon CP, Savage-Elliott I, Kennedy JG. Establishing proof of concept: platelet-rich plasma and bone marrow aspirate concentrate may improve cartilage repair following surgical treatment for osteochondral lesions of the talus. World J Orthop 3:101–108, 2012.
32. Kuettner KE, Cole AA. Cartilage degeneration in different human joints. Osteoarthritis Cartilage 13:93–103, 2005.
33. Cole AA, Margulis A, Kuettner KE. Distinguishing ankle and knee articular cartilage. Foot Ankle Clin 8:305–316, 2003.
34. Zengerink M, Szerb I, Hangody L, Dopirak RM, Ferkel RD, van Dijk CN. Current concepts: treatment of osteochondral ankle defects. Foot Ankle Clin 11:331–359, 2006.
35. Baums MH, Heidrich G, Schultz W, Steckel H, Kahl E, Klinger HM. Autologous chondrocyte transplantation for treating cartilage defects of the talus. J Bone Joint Surg Am 88:303–308, 2006.
36. Gobbi A, Francisco RA, Lubowitz JH, Allegra F, Canata G. Osteochondral lesions of the talus: randomized controlled trial comparing chondroplasty, microfracture, and osteochondral autograft transplantation. Arthroscopy 22:1085–1092, 2006.
37. Kreuz PC, Steinwachs M, Erggelet C, Lahm A, Henle P, Niemeyer P. Mosaicplasty with autogeneous talar autograft for osteochondral lesions of the talus after failed primary arthroscopic management: a prospective study with a 4-year follow-up. Am J Sports Med 34:55–63, 2006.
38. Kumai T, Takakura Y, Higashiyama I, Tamai S. Arthroscopic drilling for treatment of osteochondral lesions of the talus. J Bone Joint Surg Am 81:1229–1235, 1999.
39. Taranow WS, Bisignani GA, Towers JD, Conti SF. Retrograde drilling of osteochondral lesions of the medial talar dome. Foot Ankle Int 20:474–480, 1999.
40. Anitua E, Sanchez M, Nurden AT, Orive G, Andìa I. New insights into and novel applications for platelet-rich fibrin therapies. Trends Biotechnol 24:227–234, 2006.
41. Anitua E, Sanchez M, Nurden AT, Zalduendo M, De la Fuente M, Azofra J, Andìa I. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. Rheumatology 46:1769–1772, 2007.
42. Arnoczky SP, Anderson L, Fanelli G, Ho S, Mishra A, Sgaglione N. The role of platelet-rich plasma in connective tissue repair. Orthopedics Today 26:29, 2009.
43. Vannini F, Di Matteo B, Filardo G. Platelet-rich plasma to treat ankle cartilage pathology—from translational potential to clinical evidence: a systematic review. J Exp Orthop 2:2, 2015.