International Orthopaedics (2021) 45:2423–2428
https://doi.org/10.1007/s00264-021-05112-3

INVITED PAPERS

Outcomes of iliac crest bone marrow aspirate injection for the treatment of recalcitrant Achilles tendinopathy

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Received: 1 June 2021 / Accepted: 10 June 2021 / Published online: 13 July 2021

Abstract

Background Achilles tendinopathy is a common cause of posterior ankle and heel pain in both active and sedentary patients. Though the majority of patients respond to first-line non-operative management including activity modification, immobilization, orthotics, and physical therapy with stretching and eccentric strengthening, there is no consensus for patients who fail these treatments. We evaluate the role of iliac crest bone marrow aspirate (BMA) injections as a treatment option for recalcitrant cases.

Methods A retrospective chart review was conducted of patients with refractory Achilles tendinopathy treated with iliac crest BMA concentrate injection. Symptoms were assessed using the numeric rating system (NRS) pain score at the pre-operative visit and at six, 12, 24, and 48 weeks postoperatively. Post-operative complications were recorded.

Results A total of 15 patients (15 feet) with recalcitrant Achilles tendinopathy (5 insertional, 8 non-insertional, 2 combined) treated with iliac crest BMA concentrate injections were included in the study. Average age was 53.2 years (range, 25 to 64), average BMI was 27.1 kg/m^2 (range, 18.4 to 34.4), and average duration of symptoms prior to BMA injection was 2.3 years (range, 1 to 7). Pre-operatively, average NRS was 6.26 (95% CI, 5.04 to 7.49), with significant improvement at six weeks (mean, 4.26; 95% CI, 2.94 to 5.59; p = 0.04), ten weeks (mean, 4.13; 95% CI, 2.91 to 5.35; p = 0.012), 24 weeks (mean, 3.40; 95% CI, 2.05 to 4.75; p = 0.03), and 48 weeks (mean, 2.60; 95% CI, 1.14 to 4.06; p = 0.007) post-operatively. Overall, there was trending improvement over the 48-week follow-up period, with a mean improvement in NRS of − 3.22 (95% CI, − 1.06 to − 5.38; p = 0.007) at final follow-up. There was no discernable difference between insertional and non-insertional tendinopathy, and there were no incidences of post-operative complications.

Conclusion Iliac crest BMA appears to be a safe, effective, and potentially lasting treatment option for patients with intractable, insertional and non-insertional Achilles tendinopathy. Patients demonstrated and maintained statistically significant decrease in NRS pain score post-operatively with no complications at the donor or injection site.

Keywords Achilles tendinopathy · Iliac crest bone marrow aspiration · Bone marrow aspirate · BMAC · Stem cells

Level of evidence: IV, case series

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Introduction

Achilles tendinopathy is a common tendon disorder affecting both active and sedentary individuals [1]. Elite athletes have a 24% lifetime incidence of Achilles tendinopathy, with 18% of them experiencing symptoms before the age of 45 [2]. Furthermore, Achilles tendon disorders develop in 6.8% of military recruits [2, 3] and 9% of recreational runners [4]. Patients may present with Achilles tendon pain and swelling, particularly when taking the first steps upon waking up and upon rising after prolonged sitting [5].

Non-insertional tendinopathy more frequently affects a hypovascular area of the Achilles tendon, located approximately 2 to 6 cm proximal to the calcaneal insertion [5]. Risk factors include running, patients with systemic inflammatory diseases, such as lupus and rheumatoid arthritis, and patients with a history of fluoroquinolone antibiotic or corticosteroid usage [5, 6]. Other risk factors, such as diabetes, obesity, hypertension, oral contraceptives, and hormone replacement therapy, likely increase risk by inhibiting blood flow to the Achilles tendon [5]. Hindfoot pronation has also been associated with a higher risk of mechanical damage of the Achilles tendon [7]. Non-insertional Achilles tendinopathy often responds to conservative treatments including activity modification, immobilization, orthotics, and physical therapy with eccentric stretching and strengthening [8]. Despite frequent success with the non-operative treatment, up to 30% of patients will have persistence or recurrence of symptoms [8, 9].

Biologic treatment agents, including bone marrow aspirate (BMA) concentrate, has attracted interest as a possible treatment for tendon disorders, including recalcitrant Achilles tendinopathy, using patient's own biological repair mechanisms to improve healing and prevent the need for more invasive treatments. Iliac crest BMA may facilitate tendon healing through the injection of concentrated fluid rich in pro-inflammatory elements, progenitor mesenchymal, endothelial, and haematopoietic cells.

The purpose of this study is to review our experience with iliac crest BMA injection for the treatment of chronic Achilles tendinopathy unresponsive to conservative treatment modalities. We hypothesized that, with this new treatment modality, patients would experience less pain with a low incidence of adverse events.

Materials and methods

Institutional review board approval was obtained for this retrospective study. We included consecutive patients diagnosed with insertional and non-insertional Achilles tendinopathy with symptoms lasting for at least 12 months who failed non-operative treatment and subsequently underwent surgical treatment with BMA concentrate injection between 2011 and 2017. Insertional Achilles tendinopathy was defined by the presence of localized pain and tenderness at the insertion of the Achilles tendon onto the calcaneus, while non-insertional Achilles tendinopathy was defined by the localized symptoms at roughly 6 to 7 cm proximal to the insertional site. All patients failed a combination of non-operative treatment modalities, including physical therapy with specific Achilles tendon stretching and eccentric strengthening exercises, pain management including anti-inflammatory medications, orthotics, and boot immobilization. Patients were excluded if they underwent concomitant procedures at the time of BMA injection, if they received a corticosteroid, platelet-rich plasma (PRP), or another orthobiologic injection within three months of the BMA injection, or if they had a prior history of surgery to the involved Achilles.

Patient-reported symptoms were assessed using the numeric rating system (NRS) pain scale, in which patients were asked to rate their pain intensity on a scale of 0 to 10, with zero representing "no pain" and ten representing "worst possible pain." The NRS was assessed at the pre-operative office visit and at six, ten, 24, and 48 weeks following the BMA injection. Post-operative complications including surgical and donor site morbidity following injection were also recorded.

Surgical procedure

All patients underwent the same surgical treatment by the senior author. Bone marrow aspiration was performed in the operating room with the patient under sedation by the anaesthesia team. A subcutaneous injection of 5 cc of a 1:1 mixture of 1% lidocaine and 0.5% marcaine without epinephrine was performed at the iliac crest site. A 1-mm incision was made over the ipsilateral iliac crest 3 cm lateral to the anterior superior iliac spine. A bone marrow aspirate needle (Biomet Biologics, Warsaw, IN) was placed into the iliac wing. The trephine trochar with side fenestrations was tapped in between the inner and outer tables of the pelvis to a depth of 4–5 cm (Fig. 1). The trochar was then withdrawn and bone marrow was aspirated into a 60-mL syringe preloaded with 4 mL of anticoagulant citrate dextrose solution (Fig. 2). Aliquots of 5 mL were aspirated before withdrawing and rotating the trephine 5–10 mm. After 20 mL and 40 mL were collected, the trajectory of the trephine was redirected by reinserting the trochar and tapping the device into the bone for 4–5 cm depth (Fig. 3). This aspirate was then concentrated in a specialized chamber using the GPSIII system (Biomet Biologics, Warsaw, IN) by centrifugation

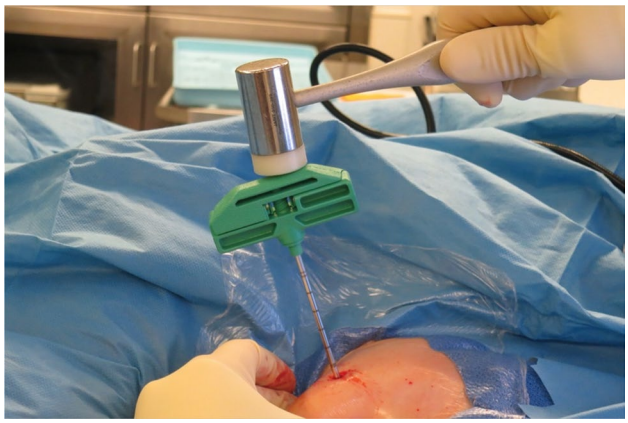

Fig. 1 A bone marrow aspirate needle with a trephine trochar was tapped in the iliac wing between the inner and outer tables of the pelvis to a depth of 4–5 cm

Fig. 2 The trochar was withdrawn and a 60-mL syringe preloaded with 4 mL of anticoagulant citrate dextrose solution was attached to the needle

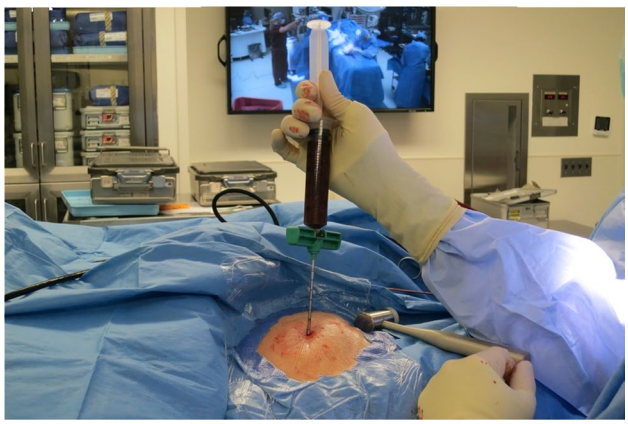

Fig. 3 Bone marrow aspirate harvesting: 5-mL aliquots were aspirated and the trajectory of the needle was adjusted every 20 mL until a total of 55 mL of aspirate was achieved

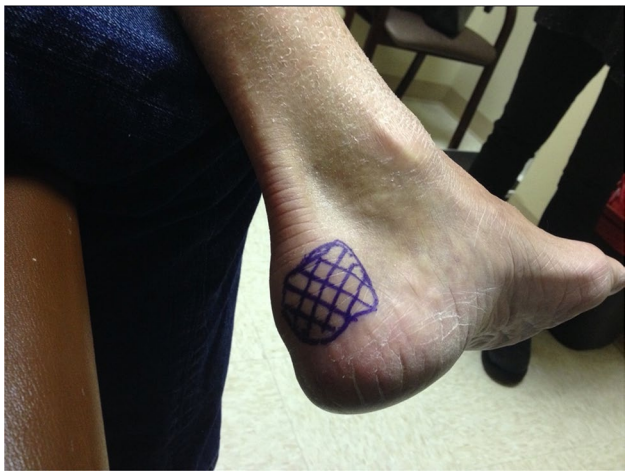

Fig. 4 Example of pre-operative identification of patient's zone of maximal tenderness in the Achilles tendon

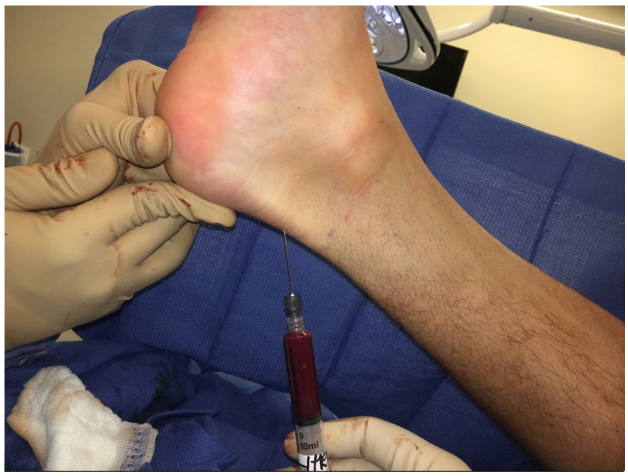

Fig. 5 The concentrated BMA was injected into the zone of maximal tenderness on the Achilles tendon, as identified pre-operatively

for 20 min at 3200 revolutions per minute. Approximately 6 mL of concentrated bone marrow aspirate was obtained.

The concentrated BMA was injected into the zone of maximal tenderness at the Achilles, which was identified pre-operatively (Figs. 4 and 5). Through a medial percutaneous approach, avoiding the course of the sural nerve posterolaterally, the entire zone of the painful tendon was injected using a 25-gauge needle, with skin piercings at 5-mm intervals and injections at different depths and directions. After withdrawing the needle, digital pressure was held over each penetration point to prevent retrograde flow of the injected BMA. A sterile compression dressing was then applied.

Post-operatively, patients remained in a cast for two weeks, with a limited weight-bearing protocol and crutches or cane assistance, avoiding any aggravating activities. Two

weeks after surgery, patients were allowed to weight bear as tolerated in a boot brace. At six weeks post-operatively, patients were allowed to discontinue the use of the boot brace and progressively return to activities as tolerated.

Statistical analysis

One-way repeated measures analysis of variance was used to compare NRS scores prior to BMA injection with NRS scores at six, 12, 24, and 48 weeks following injection. Statistically significant values were defined with a p-value of less than 0.05. All statistical analysis was performed using SPSS version 22 (IBM SPSS Statistics, Coppell, TX).

Results

In total, 15 feet in 15 patients met the inclusion and exclusion criteria and constituted our study cohort. Six (40%) of these patients were male and 16 (60%) were female, with an overall mean age of 53.2 years (range, 25 to 64) and mean body mass index (BMI) of 27.1 kg/m^2 (range, 18.4 to 34.4). There were five (33%) patients with insertional, eight (53.3%) patients with non-insertional, and two (13.3%) patients with both insertional and non-insertional Achilles tendinopathy. Pre-operatively, patients had symptoms for an average of 2.3 years (range, 1 to 7 years).

Clinical outcomes

The average pre-operative NRS pain score was 6.26 (95% CI, 5.04 to 7.49). There was a sustained, statistically significant improvement in NRS at six weeks (mean, 4.26; 95% CI, 2.94 to 5.59; p = 0.04), ten weeks (mean, 4.13; 95% CI, 2.91 to 5.35; p = 0.012), 24 weeks (mean, 3.40; 95% CI, 2.05 to 4.75; p = 0.03), and 48 weeks (mean, 2.60; 95% CI, 1.14 to 4.06; p = 0.007) post-operatively (Table 1). Overall, there was trending improvement over the 48-week follow-up period, with a mean improvement in NRS of − 3.22 (95% CI, − 1.06 to − 5.38; p = 0.007) at final follow-up (Fig. 6).

When comparing outcomes between patients with insertional, non-insertional, and combined Achilles tendinopathy, there were no statistically significant differences observed in the NRS pain score.

There were no post-operative complications reported, including incidence of donor site morbidity, persistent pain at the iliac crest, wound infection, haematoma, or heterotopic ossification at the injection site.

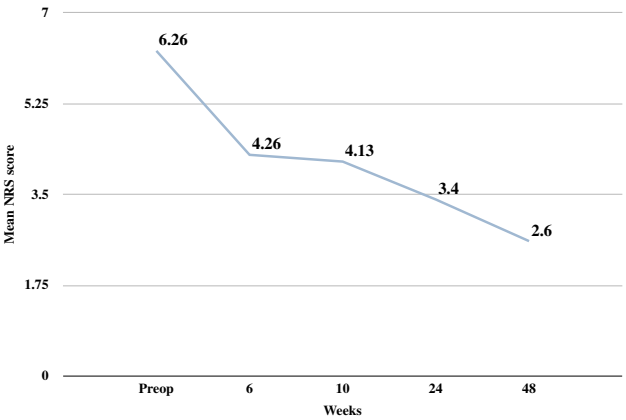

Fig. 6 Graphic plot of mean NRS pain scores at each time point. NRS, numeric rating system

Discussion

We evaluated our experience of 15 cases of intractable insertional and non-insertional Achilles tendinopathy in 15 patients treated with iliac crest bone marrow aspirate concentrate injection. Our results demonstrated a persistent, significant decline in NRS pain scores with trending improvement post-operatively. In addition, we observed no adverse events associated with BMA injection in our study cohort.

Most cases of insertional and non-insertional Achilles tendinopathy can be managed without operative treatment. Conservative modalities include activity modification, immobilization, orthotics, and physical therapy with tendon stretching and eccentric strengthening [8]. Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used for symptomatic relief, although the effectiveness has not yet been demonstrated in a randomized controlled study [10].

Table 1 Paired differences in mean NRS pain scores between pre-operative and each follow-up time period. *P-values < 0.05. *NRS*, numeric rating system; *CI*, confidence interval

NRS	Mean	Paired differences		p-value
		Difference from preoperative	95% CI of the difference	
Preoperative	6.26	0	0	0
6 weeks postoperative	4.26	− 2.67	− 1.03 to − 4.32	0.004*
10 weeks postoperative	4.13	− 1.80	− 0.48 to − 3.14	0.012*
24 weeks postoperative	3.40	− 2.47	− 0.99 to − 3.94	0.003*
48 weeks postoperative	2.60	− 3.22	− 1.06 to − 5.38	0.007*

While traditional non-invasive treatments have demonstrated some success in alleviating symptoms, studies have shown that up to 30% of patients have recurrence of symptoms or find conservative treatments ineffective [8, 9]. In addition, corticosteroid injections in the Achilles tendon produce short-term pain relief [11] and are generally contraindicated due to a significant risk for tendon rupture [5]. Other non-operative options include extracorporeal shock wave therapy, chemical or electrocoagulation-induced sclerosis, topical glyceryl trinitrate, and serine protease inhibitor injections [8].

In patients unresponsive to conventional treatment modalities, orthobiologic therapy has emerged as a new potential option. Histologically, the Achilles tendon demonstrates chronic degeneration rather than inflammatory changes [5], which can be caused by an inability of the tendon cell matrix to repair itself following repetitive microtrauma [12]. Therefore, the application of pro-inflammatory cytokines, growth factors, and stem cells may improve healing, facilitating angiogenesis, chemotaxis, and cell proliferation [13].

Prior biologic studies have focused on the use of peripherally drawn PRP to stimulate tendon healing. Guelfi and colleagues reported their findings in a cohort of 73 patients receiving PRP for non-insertional Achilles tendinopathy with 91.6% of patients reporting satisfactory results. However, in a Cochrane review evaluating 19 clinical trials of platelet-rich therapies in musculoskeletal injuries, including one trial of Achilles tendinopathy, the authors concluded that there was insufficient evidence to support the use of PRP for orthopaedic injuries [14]. A systematic review by Vannini et al. presented a similar conclusion that the current literature does not support the use PRP injections for the treatment of foot and ankle pathology [15]. de Vos and colleagues randomized 54 patients with chronic non-insertional Achilles tendinopathy into treatment groups consisting of an eccentric exercises protocol with ultrasound-guided injection of either PRP or saline. The authors reported improvements in the Victorian Institute Sports Assessment-Achilles (VISA-A) score, satisfaction, and return to sports with no statistically significant difference between the two treatment arms at 24 weeks post-operatively [16]. In another study with similar interventions and one year follow-up, de Jonge and colleagues demonstrated no difference in pain reduction in placebo and PRP treatment groups, with 59% of patients in both groups reporting satisfaction with their respective treatment [17].

Concentrated BMA injection is thought to stimulate a superior healing response compared to PRP alone, which lacks progenitor stem cells. In addition to platelet-derived growth factors, the bone marrow aspirate contains mesenchymal and haematopoietic stem cells in addition to endothelial and other progenitor cells. A drawback of BMA use is the fact that it requires an operative harvesting of stem cells by drilling into the iliac crest. This requires exposure of patients to anesthesia and introduces potential risk for complications including donor site morbidity.

An experimental study in rabbits compared the efficacy of PRP and BMA concentrate injections on wound healing. The study concluded that there was improved healing in the BMA group compared to the PRP group. Additionally, cells in the BMA group demonstrated continued activity at four weeks after the injection while there was no detectable cell activity in the PRP group after two weeks [17]. Furthermore, in an experimental collagenase-induced rat model of Achilles tendinopathy, the use of tendon-derived stem cells injected in association with PRP doubled the effectiveness of tendon healing when compared to the isolated use of PRP [18].

To the authors' knowledge, no clinical studies have evaluated the efficacy of BMA in stimulating the healing response in patients with chronic tendinopathy. Stein et al. reported no adverse effects or re-ruptures in patients with acute Achilles tendon ruptures treated with surgical repair and adjuvant BMA injections, and acknowledged the potential for earlier ankle mobilization in these patients [19].

Our study has several limitations that include a retrospective analysis and the lack of a control group. In addition, our study cohort consisted of a relatively small number of patients with short-term follow-up. However, we were able to demonstrate with serial postoperative follow-up over the course of 48 weeks that patients had a significant, quantifiable improvement in symptoms with trending improvement over time. Similarly, while our data suggests that BMA injection is efficacious in both insertional and non-insertional, our study cohort may have likely been unpowered to detect a true difference between the two groups. Future prospective, randomized controlled studies, with functional follow-up are needed to better define the role of BMA concentrate injections and related orthobiologics in the treatment of recalcitrant Achilles tendinopathy.

In conclusion, our study of the clinical role of bone marrow aspirate injections in the treatment of recalcitrant Achilles tendinopathy found a statistically significant decrease in NRS pain score at 48-week follow-up when compared to preoperative measurements. Furthermore, we found the procedure to be safe with no adverse effects noted in our cohort.

Author contribution All authors contributed to the design of the study, literature review, data gathering and interpretation, manuscript writing, and editing.

Data availability All data available for this study was reported in the manuscript.

Code availability Not applicable.

Declarations

Ethics approval This study was approved by Institutional Review Board (IRB), under number MODCR00000491.

Consent to participate All participants signed informed consent to participate in the study.

Consent for publication All participants signed informed consent allowing publication of deidentified data.

Conflict of interest The authors declare no competing interests.

References

1. Longo UG, Ronga M, Maffulli N (2018) Achilles tendinopathy. Sports Med Arthrosc Rev 26:16–30
2. Kujala UM, Sarna S, Kaprio J (2005) Cumulative incidence of Achilles tendon rupture and tendinopathy in male former elite athletes. Clin J Sport Med 15:133–135
3. Milgrom C, Finestone A, Zin D, Mandel D, Novack V (2003) Cold weather training: a risk factor for Achilles paratendinitis among recruits. Foot Ankle Int 24:398–401
4. Lysholm J, Wiklander J (1987) Injuries in runners. Am J Sports Med 15:168–171
5. Weinfeld SB (2014) Achilles tendon disorders. Medical. Clinics 98:331–338
6. Parmar C, Meda K, Hennessy M (2007) Achilles tendon rupture associated with combination therapy of levofloxacin and steroid in four patients and a review of the literature. Foot Ankle Int 28:1287–1289
7. Holmes GB, Lin J (2006) Etiologic factors associated with symptomatic Achilles tendinopathy. Foot Ankle Int 27:952–959
8. Lopez RGL, Jung H-G (2015) Achilles tendinosis: treatment options. Clin Orthop Surg 7:1
9. Paavola M, Kannus P, Paakkala T, Pasanen M, Järvinen M (2000) Long-term prognosis of patients with Achilles tendinopathy. Am J Sports Med 28:634–642
10. Åström M, Westlin N (1992) No effect of piroxicam on Achilles tendinopathy: a randomized study of 70 patients. Acta Orthop Scand 63:631–634
11. Gill SS, Gelbke MK, Mattson SL, Anderson MW, Hurwitz SR (2004) Fluoroscopically guided low-volume peritendinous corticosteroid injection for Achilles tendinopathy: a safety study. JBJS 86:802–806
12. Leadbetter WB (1992) Cell-matrix response in tendon injury. Clin Sports Med 11:533–578
13. de Mos M, van der Windt AE, Jahr H, van Schie HT, Weinans H, Verhaar JA, van Osch GJ (2008) Can platelet-rich plasma enhance tendon repair? A cell culture study. Am J Sports Med 36:1171–1178
14. Moraes VY, Lenza M, Tamaoki MJ, Faloppa F, Belloti JC (2013) Platelet-rich therapies for musculoskeletal soft tissue injuries. Cochrane Database Syst Rev (12):CD010071. https://doi.org/10.1002/14651858.CD010071.pub2
15. Vannini F, Di Matteo B, Filardo G, Kon E, Marcacci M, Giannini S (2014) Platelet-rich plasma for foot and ankle pathologies: a systematic review. Foot Ankle Surg 20:2–9
16. de Vos R-J, Weir A, Tol J, Verhaar J, Weinans H, Van Schie H (2011) No effects of PRP on ultrasonographic tendon structure and neovascularisation in chronic midportion Achilles tendinopathy. Br J Sports Med 45:387–392
17. de Jonge S, de Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Tol JL (2011) One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. Am J Sports Med 39:1623–1630
18. Chen L, Liu J-P, Tang K-L, Wang Q, Wang G-D, Cai X-H, Liu X-M (2014) Tendon derived stem cells promote platelet-rich plasma healing in collagenase-induced rat Achilles tendinopathy. Cell Physiol Biochem 34:2153–2168
19. Stein BE, Stroh DA, Schon LC (2015) Outcomes of acute Achilles tendon rupture repair with bone marrow aspirate concentrate augmentation. Int Orthop 39:901–905