Chapter 13
Regenerative Medicine for the Foot and Ankle

Emily N. Fatakhov, Tina Bijlani, and Richard G. Chang

The foot is comprised of 28 bones, including 14 phalanges, 7 tarsal bones (talus, calcaneus, cuboid, navicular, and three cuneiforms), 5 metatarsals, and 2 sesamoids. Functionally, the foot is divided into three distinct sections. The hindfoot consists of the talus and calcaneus with the proximal ankle mortise connecting the tibia and fibula to the talus. The subtalar joint refers to the connection between the talus and calcaneus. The distal portion of the talus and calcaneus connects to the midfoot, known as the midtarsal or Chopart joint. The navicular, cuneiforms, and cuboid form the midfoot, a pyramid-like collection of bones, connecting the proximal metatarsals at the Lisfranc joint. Lastly, the forefoot contains everything distal to the Lisfranc joint, which includes the metatarsals, sesamoids, and phalanges. The hallux (big toe) contains two phalanx bones, distal and proximal. This articulates with the head of the first metatarsal forming the first metatarsophalangeal joint (MTPJ) [30]. Under the first metatarsal head lay two small round bones, the sesamoids.

The ankle (talocrural) joint is a synovial joint formed by the tibia, fibula, and talus. It is a hinge joint permitting dorsiflexion and plantar flexion, while eversion and inversion are produced by the subtalar joint. Multiple ligaments in the ankle provide support and resistance to specific movements including the tibiofibular, deltoid, and anterior and posterior talofibular and calcaneofibular ligaments. The Achilles tendon is the common tendon for the plantaris, gastrocnemius, and soleus with attachment to the calcaneus permitting plantar flexion of the foot. The peroneus (fibularis) longus and brevis tendons course posterior to the lateral malleolus and provide eversion and plantar flexion, while the peroneus tertius runs anterior to the lateral malleolus and provides eversion and dorsiflexion. Medially, the tarsal

E. N. Fatakhov · T. Bijlani
Rehabilitation Medicine, The Mount Sinai Hospital, Mount Sinai, New York, NY, USA

R. G. Chang (✉)
Department of Rehabilitation & Human Performance, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: Richard.Chang@mountsinai.org

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tunnel contains the tibialis posterior, flexor digitorum longus and flexor hallucis longus tendons, posterior tibial artery, vein, and tibial nerve [30, 31].

Conventional treatment for musculoskeletal injury focuses on reducing inflammation and pain to provide symptomatic relief. However, it is now known that inflammation is an integral part of the healing process. These medications may impair the healing of damaged tissues, leading to chronic degenerative disruption and several adverse effects [28].

Plantar Fasciitis

The plantar fascia is a thick ligamentous connective tissue that originates from the heel at the calcaneus and runs out to attach to the ball of the foot at the bases of the five metatarsal heads. The aponeurosis consists of three bands: lateral, medial, and central. The central band originates from the medial tubercle of the calcaneus and travels to the five toes. At the metatarsal head, the central band divides into five slips, each of which inserts at the proximal phalanx of each toe. It has a static purpose, in which it supports the arch of the foot via tensioning and load bearing, as well as a dynamic purpose, in which it alternately elongates and contracts during the gait cycle, enabling the arch to flatten and elevate [25].

Plantar fasciitis (or plantar fasciosis/fasciopathy) is one of the most common causes of heel pain and is characterized by inflammation or degeneration of the plantar fascia [25]. In the United States, plantar fasciitis affects about two million people per year with an equal incidence between males and females. This results in approximately 1,000,000 patient visits per year and accounts for 10% of injuries in runners [25]. Plantar fasciitis results when increased load to the plantar fascia eventually leads to micro-tearing, inflammation, and pain. Scar tissue then damages the fascia, and with this increased force, heel spurs are prone to develop where the fascia attaches to the calcaneus. Rupture of the plantar fascia may sometimes occur. Pain usually begins when patients report a new repetitive activity, change in footwear, or walking on harder than usual surfaces [22]. Initially they may present with heel or midfoot pain, typically worse upon waking in the morning and again at the end of the day after increased activity. There are three different phases of pathology. The initial acute onset lasts up to 4 weeks, the subacute phase lasts up to 3 months, and afterward it is considered a chronic condition, at which point inflammation is replaced by degenerative changes, and tension enthesophytes often develop at the calcaneal insertion.

Per current evidence-based guidelines, treatment varies based on the timing of symptoms and clinical phase. In the acute phase, stretching of the plantar fascia and Achilles tendon, either manually or by rolling the foot over a tennis ball or a water bottle, is recommended [24]. Symptomatic relief may also be accomplished with the application of ice or by administering oral nonsteroidal anti-inflammatory drugs or acetaminophen [24]. Other options include heel cushions to act as shock absorbers, orthotic arch supports to alleviate stress of the plantar fascia, taping to

decrease mobility of the joint, posterior night splints, and iontophoresis [25]. When symptoms progress to the subacute phase, ultrasound-guided corticosteroid injections, acupuncture, and manual therapy are recommended [23, 27]. Once it reaches the chronic phase, extracorporeal shock wave/sound therapy has yielded promising results [25, 27]. Botulinum toxin A is another, possible injectable treatment method that has shown some promise in some case series [20–22]. There are several instances in which conservative measures fail or patients do not opt for a surgical intervention. Alternatively, patient may not tolerate the side effects associated with medications. Nonsteroidal anti-inflammatory medications, via inhibition of the cyclooxygenase pathway, can potentiate damage to the gastrointestinal mucosa, resulting in peptic ulcer disease and gastrointestinal bleeding [28]. Glucocorticoids are associated with systemic increased risk for diabetes, glaucoma, and suppression of the hypothalamic-pituitary-adrenal axis, at the cellular level [26]. With these side effects and continued degenerative damage despite treatment, it is advantageous to find other treatment options for this common musculoskeletal disease. Regenerative medicine techniques can potentially help to promote remodeling of unhealthy tendinopathic tissue to healthy tendon but more importantly aid in decreasing the inflammatory environment [79, 80]. Several studies have shown improvement in pain and function with platelet-rich plasma injections utilized to treat plantar fasciitis. The injection of this centrifuged, autologous blood may provide cellular and humoral mediators to induce healing of degenerated tissues.

In a single-center, unblinded, prospective, preliminary study, Martinelli et al. demonstrated the safety of PRP injections when utilized for the treatment of chronic plantar fasciitis. Fourteen consecutive patients with chronic plantar fasciitis unresponsive to at least 3 months of icing, NSAIDs, and stretching received three once weekly, palpation-guided injections of PRP into the plantar fascia and were assessed 12 months after the procedure. The modified Roles and Maudsley (RM) score and a visual analogue scale (VAS) were used to evaluate the clinical results. At a year follow-up, results were rated as excellent in the majority of patients (9, 64.3%). The remaining 14.3% of patients rated results as good, acceptable in 14.3%, and poor in 7.1%. VAS for pain was found to be significantly decreased from 7.1 ± 1.1 before treatment to 1.9 ± 1.5 at 12 months follow-up with $p < 0.01$ [29].

In a prospective study by Kumar et al., 44 patients (50 heels) who had not responded to at least 1 year of standard conservative management were offered a one-time PRP injection. RM, VAS, and American Orthopedic Foot and Ankle Society (AOFAS) scores were collected prior to the procedure, at 3 months, and at 6 months. The PRP group was shown to have efficacy in these chronic cases. At 6-month review, RM scores improved from mean 4 to 2 ($p < 0.001$), VAS improved from 7.7 to 4.2, and AOFAS improved from 60.6 to 81.9. The study was without complication, and 28 patients (64%) were very satisfied, indicating they would opt for the injection again [6].

This was further demonstrated in a randomized controlled trial by Gill et al. with 179 patients who had greater than 6 months of pain due to plantar fasciitis (91 in treatment group and 88 in control group). For patients receiving the PRP, 10 ml of patient's blood was collected, mixed with 2 ml acid citrate dextrose (anticoagulant),

and placed in Autologous Platelet Separator System, to yield PRP. Under sterile conditions, patients received 3 ml of PRP into the plantar fascia at site of maximum tenderness. Patients were followed at week 2, 4, 8, 12, and 52, during which VAS was utilized to assess pain relief. The mean VAS score in case group (PRP) decreased from baseline 6.6 to 0.54 at 52-week follow-up. This indicates that PRP may significantly improve pain in patients with chronic plantar fasciitis. Additionally, complication rates were minimal and symptom recurrence rate low [19].

A recent double-blinded, prospective randomized controlled trial (RCT) with 75 patients showed that PRP was as effective or more effective than corticosteroid injection when compared with normal saline injection control to reduce pain over 3 months of follow-up and improve functional scores for chronic plantar fasciitis [4]. Mahindra et al. found significant improvement in VAS and AOFAS in the PRP and corticosteroid group at 3-week and 3-month follow-up, while there was no improvement in the placebo group. PRP proves to have less side effects in comparison to traditional steroid injection, which may be unsafe for diabetics and those with multiple comorbidities. Glucocorticoids (GCs), the most important and frequently used class of anti-inflammatory drugs, are associated with diabetes, glaucoma, and suppression of the hypothalamic-pituitary-adrenal axis, at the cellular level [26]. Its potent anti-inflammatory and immunosuppressive actions allow it to remain the mainstay of treatment. However, with its multiple negative associations, it is vital to become equipped with alternate treatment strategies.

The effects of PRP not only showed improvements in pain but also showed a longer duration of benefit when compared to other current treatments. In a 2018, level I randomized controlled prospective study of 158 patients by Uğurlar et al., the therapeutic effects of four different treatment methods for chronic plantar fasciitis with a symptomatic heel spur not improved with 6 months of conservative treatment (including NSAIDs, orthotics, and gastrocnemius-soleus muscle stretching and confirmed on ultrasound imaging) were compared. Patients were randomized to one of four treatment modalities, which were given once a week for 3 weeks: extracorporeal shock wave therapy, platelet-rich plasma injection, local corticosteroid injection, and prolotherapy. Clinical outcomes were assessed using visual analogue scale and Revised Foot Function Index. While no significant improvements were noted in the Revised Foot Function Index, there was a discrepancy in the duration of pain relief. Corticosteroid injections were initially more effective in the first 3 months; extracorporeal shock wave therapy was found to be more effective in the first 6 months. Notably, the treatment groups with prolotherapy and platelet-rich plasma had the longest effect from 3 to 12 months [12].

Inflammation and degenerative changes were improved as evidenced by certain studies [11, 78]. In a prospective, unblinded, cohort study by Ragab et al., 25 patients with chronic plantar fasciitis were studied from Feb 2010 to June 2011. Ultrasound measurement of the medial, central, and lateral bands of the plantar fascia was done prior to injection of PRP in the affected foot and asymptomatic foot for comparison. Plantar fascial thickness greater than 4 mm was considered abnormal. Researchers injected 5 mL platelet concentrate into the most tender aspect of plantar fascia using

a peppering technique and found a decrease in plantar fascial thickness, indicating improvement of tendinopathic changes [78].

PRP was directly compared to corticosteroids and found to be either equally or more effective with fewer side effects [3, 4, 5, 8, 15]. For example, Monto's 2014, single-blinded prospective randomized study of 40 patients found a single, 3 mL PRP injection under ultrasound guidance to be superior in terms of duration and effectiveness when compared to a single 40 mg methylprednisolone injection for treatment of chronic recalcitrant, plantar fasciitis. These patients did not respond to conservative management (NSAIDs, physical therapy, bracing). AOFAS hindfoot scores in the PRP group remained increased (indicating improved pain and function) at 3- and 6-month time periods, as well as at 1 and 2 years compared to the corticosteroid group [3]. In a comparative, single-blinded, randomized prospective study by Jain et al., they evaluated the result of single, palpation-guided injections of 3 mL PRP versus 40 mg triamcinolone and levobupivacaine hydrochloride injectate solution in 60 heels of patients with chronic plantar fasciitis of at least 1 year (not responsive to insoles, a full course of eccentric stretching exercises, and physical therapy). They found that both PRP and corticosteroid injection groups had significant improvement in VAS and modified Roles and Maudsley scores but were not statistically significant. PRP was as effective as a steroid injection at achieving symptom relief at 3 and 6 months; however, the PRP group's beneficial effects remained sustained and were statistically significant at the 12-month follow-up interval [5].

Stress Fracture: Metatarsal, Tarsal Navicular

Stress fractures in the foot are a type of chronic overuse injury, most often seen following periods of intense exercise without adequate rest and recovery. They are classified as low (calcaneus and cuboid) or high (navicular, fifth metatarsal, and sesamoids) risk, which has the potential to progress to nonunion or complete fracture. The second and third most common location out of all stress fractures are the tarsal navicular (17.6%) and metatarsal (16.2%), respectively, therefore accounting for a significant cause of foot injury.

Stress fractures account for 0.7–20% of all injuries at sports medicine clinics [18]. The pathophysiology results from damage secondary to repetitive and excessive microtrauma, leading to acceleration of normal bone remodeling with increased osteoblast activity, the production of microfractures (caused by insufficient time for repair of bone), the creation of a bone stress injury, and eventually a stress fracture. Simply put, chronic and persistent loading leads to a cortical break [17]. Certain risk factors for stress fracture include the consumption of greater than 10 alcoholic drinks per week, excessive physical activity with limited rest periods, female athlete triad, female sex, vitamin D deficiency, recreational running more than 25 miles per week, smoking, sudden increase in physical activity, and track (running sports) [13].

Patients will present with progressively worsening pain that is exacerbated by increased activity. They may have localized bony tenderness, swelling, or erythema on examination. The current standard of care for mild stress fractures is rest with progression to activity modification within 4–8 weeks. If the fracture is more critical, the rest period may extend up to 3 months, and the patient may require internal fixation surgery [1, 16]. Rest time may vary based on classification (grade 1–4) per the Arendt and Griffith's classification scale [7, 16].

During the bone healing process, cells of the periosteum in the proximal edge of the fracture and the fibroblasts in the granulation tissue convert into chondroblasts and form hyaline cartilage. Simultaneously, the periosteal cells in the distal edge of the fracture convert to osteoblasts. These two cell types mix over the fracture and form lamellar bone, known as early callus formation, which functions to provide stability of the fracture site. Lamellar bone then converts to trabecular bone and finally to compact bone, which restores full bone strength [9].

Biologics, such as growth factors, have shown benefit when applied to muscles, tendons, and ligaments. Bone marrow aspirate concentrate contains hematopoietic and mesenchymal stem cells and osteogenic growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-B (TGF-B), and vascular endothelial growth factor (VEGF), all of which have demonstrated efficacy in fracture nonunion treatment [13]. It has been shown that when these factors are utilized during surgical treatment of certain fractures, they may improve recovery. In a case report by Adams et al., a cannulated screw was utilized for delivery of bone marrow aspirate concentrate to a stress fracture nonunion, as previously studied intraosseous delivery via large bore needles and percutaneous delivery were not as effective. The patient was able to immediately bear weight despite postoperative instructions but without hardware failure. Postoperative radiographs and CT 10 weeks after the surgery confirmed union at the fracture site [2]. The use of orthopedic biologics to accelerate healing from fractures is still unknown.

Osteochondral Lesion of the Talus

Osteochondral lesion of the talus is a defect of the chondral surface and/or subchondral bone. Injuries are associated with pain, swelling, and negative impact on quality of life. The current standard of treatment for osteochondral lesions of the talus is isolated microfracture (BMS), which is a bone marrow stimulation procedure, in which subchondral bone plate is punctured into the bone marrow. This allows generation of a blood clot with precursor cells from the subchondral bone marrow, forming fibrocartilaginous repair tissue to fill the defect [14]. In short, the microfracture creates an inflammatory response. A prospective cohort study with 101 patients by Murphy et al. compared treatment of BMS alone (n = 52) to BMS augmented with bone marrow aspirate concentrate (n = 49) in the treatment of talus OCLs. BMAC consists of hematopoietic and mesenchymal stem cells with the potential to differentiate into platelets, chondrocytes, and osteoblasts, allowing for

the proper environment for cartilage repair. It is generally harvested from the iliac crest and injected in layers into the surgical defect. In this study it was shown that patients with symptomatic osteochondral lesions who received combined treatment of microfracture plus bone marrow aspirate concentrate showed statistically significant improvement in terms of symptoms, pain, activities of daily living, sports, and quality of life [14].

In an RCT by Milano et al., the effects of autologous platelet-rich plasma combined with microfractures were evaluated in the treatment of chondral defects of 15 sheep. Macroscopic appearance was evaluated utilizing the International Cartilage Repair Society (ICRS) score. Cartilage stiffness was analyzed with electromechanical indenter, and histological appearance was scored according to modified O'Driscoll score. It was found that PRP enhanced cartilage repair after microfractures. It was found to be more effective when PRP was used as an intraoperative fibrin gel in comparison with liquid intra-articular injection. While this study included patients with chondral lesions of the medial femoral condyle, it would be interesting to study patients with osteochondral lesions of the talus.

Mei et al. took this a step further and compared the difference in short-term efficacy and safety in PRP versus hyaluronic acid for reducing pain and disability caused by osteochondral lesions. In this randomized controlled trial, 32 patients were allocated to treatment by intra-articular injections of either hyaluronic acid (HA) or PRP with efficacy being assessed via AOFAS Ankle-Hindfoot Scale (AHFS) and VAS scales. While the platelet-rich plasma treatment group led to a better outcome than the HA group indicated by better AHFS and VAS scores, both were found to have efficacy in decreasing pain and increasing function for at least 6 months [10].

Ankle Osteoarthritis

The pathophysiology of osteoarthritis includes progressive and irreversible cartilage degeneration due to the avascularity and thus inability of cartilage to heal and repair. Risk factors include mechanical, genetic, age, obesity, history of trauma, obesity, muscle weakness, component of the cartilage extracellular matrix, presence of pro-inflammatory mediators including free radicals and cytokines, and depleted local population of mesenchymal stem cells [32, 33]. The etiology of arthritis of the ankle joint most commonly occurs as post-traumatic osteoarthritis (PTOA) accounting for 20–78% of all cases of ankle OA. Within the subset of PTOA, 37% of cases are secondary to fractures, followed by recurrent ankle injuries and a history of ankle sprain [34]. Less commonly, ankle arthritis may also be secondary to degenerative OA, inflammatory arthropathies such as rheumatoid arthritis, as well as crystalloid deposition disease, mixed connective tissue disease, synovitis, and hemophilic arthropathy.

Ankle arthritis is a major cause of disability and chronic pain with resultant gait disturbance. In the foot and ankle, there is a weak correlation between abnormal imaging and patient symptoms. Physical exam reveals limited range of motion

about the ankle joint, swelling, crepitus, and joint deformity [36]. Although no consensus or guideline statement exists for the treatment algorithm of ankle arthritis, the standard of care commonly involves physical therapy and symptomatic treatment including aspiration of effusion particularly if suspected with infection, crystalloid deposition disease, or Lyme arthritis [36]. Symptomatic management often includes corticosteroid injection. After failed conservative management, surgical interventions are considered including total ankle arthroplasty or arthrodesis [35]. Regardless of intensity and duration of the response following intra-articular anesthetic or corticosteroid injection, post-procedure pain relief is predictive of positive surgical outcomes [36].

Corticosteroid injections are often performed in the foot and ankle, preferably with imaging guidance to ensure accurate needle placement, as well as recognizing the possibility of inter-joint communications [36]. A retrospective review by Grice et al. showed that intra-articular steroid injections for midfoot and hindfoot osteoarthritis provided significant short-term pain relief for 82% of patients. However, only 32% showed sustained relief for 6 months and 12% at 2 years [37]. In a prospective cohort study including 289 subjects in whom 98 of 635 joints were ankles, Furtado et al. evaluated the impact of intra-articular steroid injection on VAS scores in rheumatoid arthritis patients. Overall, this study showed improvement in rest and movement VAS score in all joints from baseline to 4 weeks. The lowest statistically significant improvement was seen in the ankle and elbow arthritis. Additionally, there was no significant improvement for ankle pain at the longer-term (12 and 24 week) follow-up [38].

Hyaluronic acid (HA) injection for the management of ankle arthritis is promising particularly in the short term; however, the evidence is limited. Cohen et al. performed a double-blinded randomized control trial including 28 patients comparing injectate of Hyalgan to saline control in the tibiotalar joint. At 3-month follow-up, this study demonstrated a statistically significant improvement from baseline in the HA participants compared with control as measured by the Ankle Osteoarthritis Scale (AOS) and Western Ontario and McMaster Universities OA Index (WOMAC); at 6-month follow-up, the trend toward improvement at 6 months was not statistically significant [39]. In a randomized control trial by DeGroot et al. using the American Orthopedic Foot and Ankle Society (AOFAS) clinical rating score in 56 patients, there was a statistically significant improvement in the HA group at 6 weeks. At the 12-week follow-up, there was a substantial increase from baseline in both groups without a statistically significant difference [40]. Murphy et al. performed a prospective evaluation of 50 patients treated with a 3-injection protocol of HA injections comparing pre- and postinjection foot and ankle outcomes (FAOS) score which showed a statistically significant improvement (48 ± 6.3 to 78 ± 5.8) [41]. In order to evaluate the efficacy, safety, and dose dependency of Orthovisc injections, Witteveen et al. found that the weekly dosing (3x1mL) injection regimen showed the best results decreasing pain at rest and during walking [42]. In a prospective RCT, comparing HA injections with 6-week exercise therapy program, Karatosun et al. showed improvement without a statistically significant difference between the groups at 12-month follow-up [77].

Platelet-rich plasma may be a promising alternative in the management of ankle OA; however, there is limited evidence with low-powered studies currently available. Angthong et al. performed a retrospective case series of 12 chronic diseases of the hindfoot and ankle injected with PRP injection (3 mL) under fluoroscopic guidance. Eight out of the 12 patients showed satisfactory results [43]. In a retrospective case series of 20 patients with ankle OA, Repetto et al. performed four weekly PRP injections which demonstrated a positive effect on pain and function, with 80% of patients reporting feeling very satisfied or satisfied. In this study, 10% of patients required surgery due to early treatment failure [44]. Fukawa et al. performed a prospective case series of 20 patients with ankle OA administered with three ultrasound-guided PRP injections within a 2-week period. The results showed pain reduction on the VAS scale from 59.7 to 42.4 at 24 weeks. Statistically significant improvement in the Self-Administered Foot Evaluation Questionnaire (SAFE-Q) was seen at 12 weeks only [45].

Mesenchymal stem cells (MSCs) have the most limited data in ankle arthritis. Various preclinical and clinical trials of MSCs suggest it is a safe and therapeutically beneficial treatment (Freitag). Emadedin et al. performed autologous bone marrow (BM)-derived mesenchymal stem cell injections in 18 patients followed over a 30-month period, 6 of whom carried a diagnosis of ankle arthritis. In these patients, the mean walking distance measured at baseline was 1010 meters and increased to 1625 m and 2333 m at 6 and 30 months, respectively. Additionally, there was an improvement in WOMAC and FAOS scores and a decreased signal intensity related to subchondral edema in 4 of the 6 ankle OA patients at 6 months post-procedure [46].

As a sequela of osteoarthritis, patients often require arthrodesis. There is promising evidence for the use of bone morphogenetic protein (BMP) and platelet-derived growth factor (PDGF) in surgical management of arthritis and traumatic ankle nonunions requiring arthrodesis. Rearick et al., in a retrospective analysis studying 48 patients deemed high risk for nonunion, administered rhBMP-2 as augmentation for bone healing during ankle fusion. The results showed 92% per case union rate and 95.1% per site union rate with mean time to union of 111 days [47]. Similarly, Fourman et al. studied 82 patients undergoing complex ankle arthrodesis; half of the patients received intraoperative rhBMP-2. Those patients who received the BMP were more likely to obtain fusion after the initial surgery (93% vs 53%), required less time wearing the frame, and showed more bone bridging on CT scan [48]. Daniels et al., in a prospective randomized study, evaluated 217 patients undergoing standard internal fixation augmented with recombinant human platelet-derived growth factor BB homodimer (rhPDGF-BB) in 75 patients and 154 control subjects who underwent autograft supplementation. This study showed 84% fusion rate in PDGF compared with 65% in autograft-treated patient [49].

Overall, the data for regenerative medicine techniques for ankle osteoarthritis is promising but is limited. Most data is available for HA with good short-term results. PRP is an alternative approach also with limited evidence and low-powered studies; MSCs have the most limited data in ankle arthritis but show encouraging results. In the surgical model, the use of supplemental growth factors in the rat model is favorable, but limited data is available in humans.

Ankle Sprain

Ankle sprains are very common musculoskeletal conditions presenting to emergency departments and primary care providers and up to 10–30% of all sports-related injuries [51]. Intrinsic risk factors include limited balance, proprioception, and dorsiflexion. The main extrinsic risk factor is the type of sport played with indoor courts constituting the highest risk [50]. The most common mechanism of injury is an inversion injury causing a lateral ankle sprain with pathology involving first the anterior talofibular ligament, then the calcaneofibular ligament, and lastly the posterior talofibular ligament. Forced eversion injuries result in a medial ankle sprain, often resulting in an avulsion fracture of the medial malleolus. A syndesmotic injury (high ankle sprain) will result in significant ankle instability and a risk factor for recurrent ankle sprain.

Standard of care for ankle sprains commonly involves PRICE (protection, rest, ice, compression, and elevation) and limited weight-bearing, NSAIDs with consideration of immobilization and bracing depending on the severity of sprain. However, the mainstay of treatment involves functional rehabilitation and consideration of surgical intervention for patients with severe sprains and who participate in high-level sports.

PRP injections for ankle sprains show limited evidence for management of acute ankle sprain. In a prospective randomized double-blinded placebo-controlled trial by Rowden et al., 37 patients with acute ankle sprain evaluated in the emergency department underwent ultrasound-guided injection of leukocyte-rich PRP with local anesthetic compared with placebo at the point of maximal tenderness. The subjects were monitored on days 0, 3, 8, and 30. No statistical difference was found in pain score or lower-extremity functional scale [52]. Laver et al. studied 16 college elite athletes with grade 3 ankle sprain and syndesmotic instability who were randomized to treatment group (two leukocyte-poor PRP injections to the anterior-inferior tibiofibular ligament (AITFL) 7 days apart) followed by rehabilitation program and control group (only rehabilitation and return to play protocol). The treatment group demonstrated shorter return to play (40.8 vs 59.6 days) and less residual pain upon return to activity (12.5% vs 62.5%). Thus far, PRP does not appear to be efficacious in the setting of acute ankle sprain [53]. There is limited evidence suggesting PRP may be beneficial in a select group of high-level athletes with acute ankle sprain with syndesmotic instability.

Achilles Tendon Pathology

Chronic/Degenerative Achilles Tendinopathy

Overuse injury of the Achilles tendon is frequent in competitive and recreational athletes, as well as inactive middle-aged individuals. Achilles tendon injuries often lead to prolonged periods of sports cessation and interfere with ADLs. Acute

Achilles pain commonly develops with an abrupt increase in activity, whereas chronic pain (over 3 months) is due to cumulative microtrauma leading to degeneration and tendinopathy often exacerbated by improper footwear, poor running mechanics (lateral heel strike with pronation, gastrocnemius-soleus dysfunction), or sustained high-impact stress [56]. Pathology and concordant pain generally develop 2–6 cm proximal to the posterior calcaneus due to the relative hypovascularity of the tendon at this point.

Acute tendinitis care involves avoiding aggravating activities, ice, a short course of NSAIDs despite the lack of inflammation on histological evaluation, and support with taping or ACE. Chronic tendinopathy is managed with rehabilitation focusing on resistance training and either eccentric exercises or heavy slow resistance training program [54, 55]. Further management options include orthotics or bracing. Conservative treatment, often lasting more than 6 months, is disappointing with 25–45% of patients eventually requiring surgery with poor postoperative results and high failure rate [56].

Owing to the limited efficacy of conservative management, regenerative medicine treatments have primarily focused on PRP, with mixed results. A handful of recent trials on patients with chronic midportion Achilles tendinopathy are reviewed below. Boesen et al. followed 60 men with chronic midportion Achilles tendinopathy for 6 months. This RCT compared three arms: (1) high-volume injection (HVI) of steroid, saline, and local anesthetic versus (2) PRP (4 injections 14 days apart) versus (3) placebo (a few drops of saline under the skin). Each treatment was combined with an eccentric-based exercise program. The participants were followed at 6, 12, and 24 weeks. Although VISA-A initially only improved in the HVI group at 6 weeks, by the final time point, HVI (22 ± 4.5) and PRP (19.6 ± 4.5) showed significant improvement compared with placebo (8.8 ± 3.3). Objective parameters included ultrasound evaluation showing a significant decrease in the tendon thickness PRP group at 12 weeks and a larger decrease in PRP and HVI compared with placebo at 24 weeks [57]. A similar randomized, double-blinded placebo-controlled single-center trial performed by DeVos et al. randomized patients to an eccentric exercise program in combination with PRP or saline injection. VISA-A data was collected at 6, 12, and 24 weeks and in a second study at 1-year follow-up; the results showed an improvement but no statistically significant difference between the groups at any time points [58, 59]. There was no difference in secondary outcomes including patient satisfaction and return to sport. Using the same study group, DeVos et al. used ultrasound to identify echo-types suggestive of pathology or healing. In both the PRP and placebo groups, there was a decrease in echo-types suggesting tendinotic tissue and an increase in echo-types suggestive of organized tendon bundles. Additionally, there was no significant change in the neovascularization from baseline [60]. Similar results were demonstrated in a pilot study by Kearney et al. comparing PRP with eccentric loading program which found no difference in VISA-A and EuroQol-5D. Krogh et al. performed an RCT with 24 patients injected with PRP versus placebo (saline). At the 3-month follow-up, there was a statistically significant increase in the tendon thickness in the PRP group. However, there were

no statistically significant differences in VISA-A score, pain at rest, pain when walking, pain when tendon was squeezed, and color Doppler activity [61].

More promising studies on PRP include Guelfi et al. who performed a retrospective study involving 83 tendons (73 patients) managed with a single PRP injection. Over follow-up duration at 3 weeks and 3 and 6 months (mean 50.1 months long term) showing significant improvement in VISA-A score, 92% of patients rated the result as satisfactory and would repeat the treatment; the remaining 8% were deemed unsatisfactory and underwent a repeat PRP injection at 6 months [62]. Monto performed a single PRP injection on 30 subjects monitoring AOFAS and evaluating tendon structure on MRI/ultrasound at 2-, 3-, 6-, 12-, and 24-month follow-up. In this study, 4 patients demonstrated intrasubstance tear, 8 showed insertional tendinopathy, and 22 showed non-insertional disease. The results showed improvement in AOFAS at 3 months and persisted through the 24-month follow-up. Pre-treatment imaging abnormalities resolved in 27/29 cases at the 6-month time point [63].

The data for mesenchymal stem cells in Achilles tendinopathy is extremely limited. A recent publication by Goldberg et al. designed a protocol for a phase IIa proof-of-concept study in which patients with chronic midportion Achilles tendinopathy will undergo MSC harvest and ultrasound-guided injection to measure safety, adverse events, as well as patient-reported and radiologic outcome measures [64].

Based on the current available literature, regenerative medicine is a promising tool for sure in chronic, degenerative Achilles tendinopathy, but routine use is not supported by the literature. The most beneficial results are seen in use of PRP and improvement in MRI/US parameters suggesting improved tendon healing. However, patient-reported subjective parameters including pain and function are not greatly improved with PRP.

Achilles Tendon Rupture

Achilles tendon rupture is the most common tendon rupture in the lower extremity. The incidence is approximately 18 per 100,000, most commonly occurring in adults in the third to fifth decade and affecting men 4–5× more frequently than women. Risk factors include underlying Achilles tendon pathology which has been reported in nearly 10% of ruptures, inflammatory arthritides, steroid injections, and fluoroquinolone use. Over 80% of ruptures occur during sporting activities often during sudden foot pivoting with forced plantar flexion or rapid acceleration during the push-off phase [67]. A pop or snap is often heard with a sensation of being kicked in the leg. However, it has been reported that up to ⅓ of patients with tendon rupture do not report pain [65]. Physical exam findings are notable for inability to stand on toes and plantar flex the ankle with a positive Thompson test.

Initial management includes rest, pain control, and functional bracing with consideration of operative and nonoperative modalities providing similar healing rates but slightly longer return to work in patients managed nonoperatively. Additionally,

the re-rupture rate in nonsurgical patients is nearly 40% compared with 0.5% in surgically managed patients [67]. Extensive rehabilitation is necessary to maintain ankle function.

PRP used in the nonoperative management of Achilles tendon rupture repair is limited. Kaniki et al. performed a retrospective comparative study of 145 patients including prospective (73 patients) and historical cohorts (72 patients) assessing PRP as adjunct to accelerated functional rehabilitation. This study showed no statistically significant difference between the PRP and control groups in regard to isokinetic plantar flexion strength, range of motion, calf circumference, or Leppilahti score at 1- and 2-year follow-up [66]. In a case report, Filardo et al. completed a series of PRP injections for a 34-year-old competitive basketball player with a partial Achilles tendon rupture. The first injection was performed at 6 days post-trauma, then 7 and 14 days later with slow progression to stretching and formal rehabilitation program. The patient was able to return to sport for 20 minutes 64 days after the injury and full game participation 75 days after injury. Eighteen months later, the player required no further treatment [68].

PRP has been suggested as surgical augmentation for acute tendon repair. Animal studies have shown optimistic results for augmentation with PRP in healing Achilles tendon ruptures; however the transition to the human model has not proved as efficacious. In a prospective trial by De Carli et al., 30 patients who underwent surgical tendon repair were evaluated: 15 control who underwent only surgery and 15 who underwent surgery with intraoperative administration of liquid and gelatinized PRP with repeat PRP injection 14 days post-op. Follow-up was measured at 1, 3, 6, and 24 months; there was no difference in VAS, FAOS and VISA-A scales, in isokinetic strength evaluation or ultrasound evaluation of tendon integrity. On MRI, there was a decrease in signal enhancement in the treatment group suggestive of better tendon remodeling [69]. Similarly, Zou et al. studied 36 patients with tendon rupture in a prospective RCT. In this study, the study group underwent surgical repair with PRP injected into the paratenon sheath and around ruptured tissue prior to skin suture and followed at 3, 6, 12, and 24 months. The treatment group showed better isokinetic calf strength at 3 months but not beyond. Patient-reported outcome measures showed higher SF-36 and Leppilahti scores at 6 and 12 months but no difference at 2 years [70]. In another RCT by Schepull et al., 30 patients were randomized with the treatment group receiving PRP intraoperatively; PRP had no significant effect on acute repair with regard to elasticity, heel raise index, or functional outcomes [71]. A prospective multicenter randomized placebo-controlled superiority trial is currently underway by Alsousou et al. to evaluate clinical efficacy of PRP in Achilles tendon rupture patients treated nonoperatively. The study will include 230 patients PRP vs placebo injection to the tendon rupture gap within 12 days of injury. Outcomes will include measurement of muscle-tendon function, quality of life, pain, and overall functional goals at 4, 7, 13, and 24 weeks and 24 months [72].

Although rat models using mesenchymal stem cells (MSC) for management of Achilles tendon rupture are promising, more research and data are required for humans. In the rat, Urdzikova et al. performed MSC injections during the post-op recovery period and showed increased collagen organization and improved

vascularity with the injection [73]. Two additional rat studies involving MSC-coated sutures showed increased repair strength and lower failure load [74, 75]. In the human model, Stein et al. performed a retrospective review of a prospectively collected database of Achilles tendon rupture during recreational sports-related activity and during repair with BMAC augmentation. Twenty-seven subjects (28 tendons) were identified; in these patients, there was a 0.5 ± 1.3 cm difference in mean calf-circumference, 92% returned to sport at 6 ± 2 months, and there were no re-ruptures. However, there was no control group for comparison [75].

PRP does not appear to be beneficial to the operative or nonoperative management of acute Achilles tendinopathy or tendon rupture; more studies are needed. The rat models for MSC augmentation in operative repair are promising, but more human data is required.

Peroneal Tendinopathy

Peroneal tendinopathy involving the peroneus longus or brevis commonly occurs in runners and sports which involve frequent change of direction and lateral movements. Pain is located at lateral ankle and worse with standing or walking occasionally causing a limp. There is tenderness along the tendons just posterior to the lateral malleolus. Pain is reproduced with active-resisted ankle dorsiflexion and eversion. Standard of care includes activity modification, eccentric strength or heavy load exercises, and consideration of lateral heel wedge.

To date, in one retrospective descriptive study on chronic tendinopathies, Unlu et al. recruited 214 patients who received PRP injections for tendinopathy refractory to conventional treatment with follow-up at 6 weeks and 6 months. Of these participants, 12 underwent peroneal tendon PRP injections. In these patients, there was no statistically significant improvement in the VAS scores [76].

The literature for regenerative medicine in peroneal tendinopathy is extremely limited; more studies including high-quality RCTs will be needed to clarify its role in this overuse condition.

Summary

In conclusion, regenerative medicine is a promising field of nonoperative techniques that has shown benefit in certain musculoskeletal disorders. Evidence continues to grow to demonstrate its benefits in foot and ankle conditions; however, at present, there is limited evidence for its routine use (or as a recommended first-line therapeutic option) in the comprehensive treatment and management of foot and ankle injuries. Future studies will need to clarify what type of formulations are preferred (e.g., leukocyte rich/poor if PRP or mesenchymal stem cells are superior to corticosteroid

injections, or alternatively if mesenchymal stem cell injections are superior to PRP), if their beneficial effects may be seen beyond 1 year, if such treatments may prevent and delay the need for surgical approaches, if image guidance when performing these injections are necessary and advantageous compared to palpation-guided approaches, and ultimately, if these procedures are cost-effective in the healthcare system.

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