

# Contemporary Review: The Use of Adipocyte-Derived Mesenchymal Stem Cells in Pathologies of the Foot and Ankle

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## Introduction

Stromal cells are a heterogeneous class of connective tissue cells that are integral to the function of any organ.<sup>37</sup> These cells can be obtained, isolated, and cultured from adipose tissue to generate an injectable derivative with an immunophenotype consistent with that of mesenchymal stem cells (MSCs), thus opening a variety of potential applications in regenerative medicine.<sup>12,14,33,39,40,54,56,64,66,70,71</sup> Despite a myriad of proposed benefits, specific processing and harvest protocols can lead to substantial variation in the molecular and chemical makeup of the injectate.<sup>43</sup> In orthopaedics specifically, these adipose-derived therapies have been used as an adjunct to arthroscopic knee surgery,<sup>8</sup> for the treatment of aseptic nonunion,<sup>55</sup> and for various forms of tendinopathy and acute tendon injury.<sup>51</sup>

Within foot and ankle surgery, adipose-derived mesenchymal stem cell (ADSC) application is in its infancy. Proposed applications include osteochondral lesions (OCLs) of the talus,<sup>16</sup> diabetic foot wounds,<sup>35</sup> end-stage osteoarthritis (OA) of the ankle in conjunction with arthroscopic debridement,<sup>53</sup> and as an adjunct to improve cartilage restoration after lateral displacement calcaneal osteotomy for varus ankle OA.<sup>28</sup> The purpose of the current work is to provide the foot and ankle practitioner with an understanding of the collection, isolation, and preparation of ADSCs. In addition, their potential therapeutic components and reported clinical efficacy will be reviewed.

## Collection, Isolation, and Preparation

The specific harvest site and technique for the collection of ADSCs varies. For example, in the Lipogems technique, a skin incision is made in the flank area after

injecting a tumescent solution (25 mL of 2% lidocaine and 0.5 mL epinephrine [1:1000] in 250 mL of normal saline) using a disposable 17-gauge blunt cannula connected to a Luer-lock 60-mL syringe. The tissue is then agitated followed by a 15-minute resting period to allow for adequate emulsification of the fatty tissues. The ADSCs are then harvested using a liposuction 13-gauge blunt cannula connected to a Vaclock 20-mL syringe. After processing, the final product is transferred into 10-mL syringes and can be injected into the target site.<sup>53</sup> ADSC harvesting is substantially more involved than the harvest required for other orthobiologic products, such as platelet-rich plasma, which involves a simple blood draw. Thus, considerations such as the comfort of liposuction techniques of the clinician who may be using these products are relevant to their clinical practice.

The substantial variation in the biomolecular composition of ADSC products is in large part due to the site from which they are harvested. ADSCs can be harvested from white or brown adipose tissue.<sup>13</sup> These sources differ both functionally and morphologically. Brown adipose tissue is far less abundant than white adipose tissue and is typically found in the neck, mediastinum, and interscapular areas (Figure 1).<sup>17</sup> Brown adipose tissue contains a high mitochondrial density and expresses uncoupling protein 1

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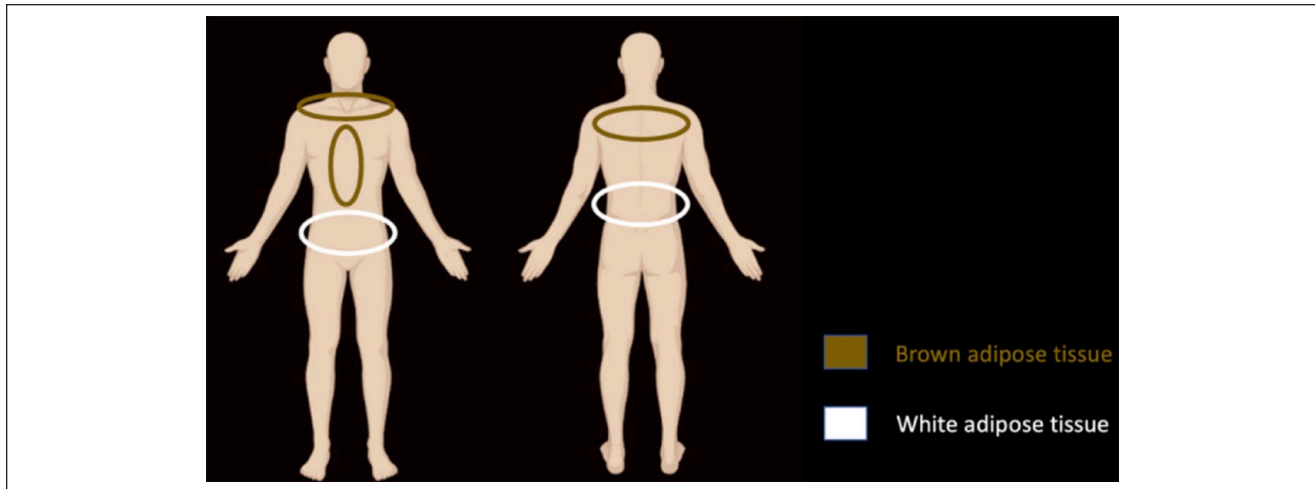
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**Figure 1.** Areas of the body with a high concentration of brown adipose tissue (circled in brown) and a high concentration of white adipose tissue (circled in white).

(UCP1), a compound regulated by adrenergic signaling through sympathetic innervations.<sup>15</sup> Thus, brown adipose tissue is largely responsible for thermogenesis. Meanwhile, white adipocytes are unilocular, contain large lipid vacuoles, and function as a store of excess energy in the form of triglycerides.<sup>57</sup>

ADSC composition can vary substantially based on brown vs white fat density in the collected sample. In murine white adipose tissue, multipotent stem cells are abundant. However, in brown adipose tissue, the stem cell number and differentiation potential are significantly reduced.<sup>49</sup> Less is known about ADSC differences between white adipose tissue and brown adipose tissue depots in humans. Preadipocyte and endothelial cell numbers have been found to differ between subcutaneous and omental white adipose depots in human subjects.<sup>61</sup> Moreover, differences in stem cell recovery have been noted based on harvest site, with greater numbers recovered from the arm when compared to the thigh, abdomen, and breast.<sup>49</sup>

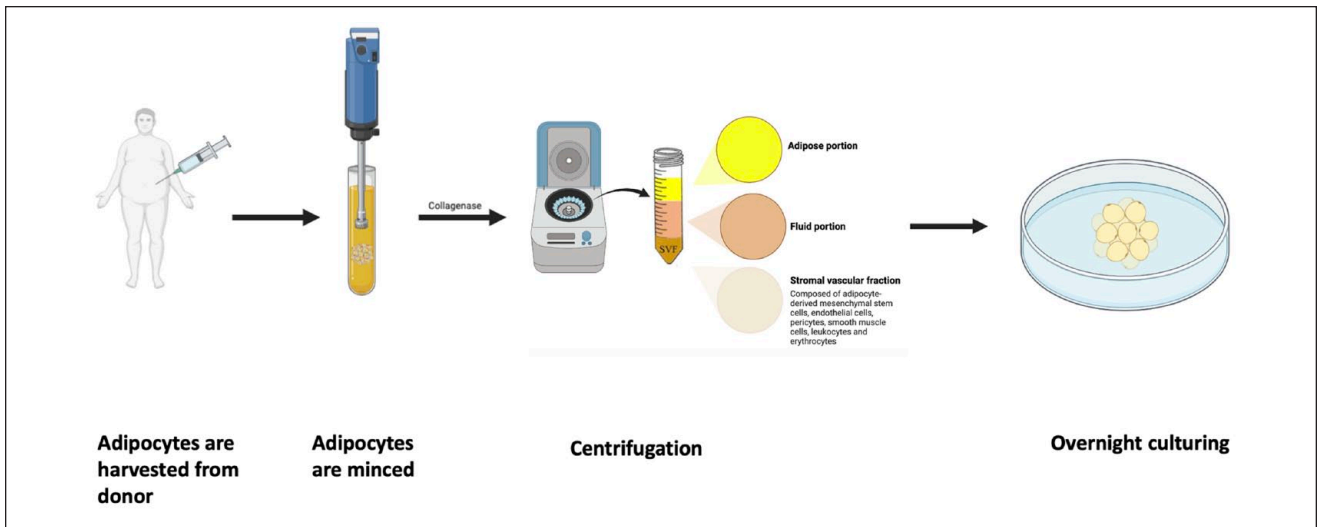
Numerous processing methodologies for ADSCs have been described, with a popular method for white adipose tissue isolation being described by Zuk et al.<sup>74</sup> In this protocol, human adipose tissue is obtained from elective liposuction via a hollow blunt-tipped cannula that is attached to gentle suction and moved through the adipose compartment to disrupt the fat tissue.<sup>74</sup> The adipose tissues are then minced, exposed to collagenase type II to undergo enzymatic digestion, and subject to centrifugation, resulting in a pellet referred to as the stromal vascular fraction (SVF).<sup>74</sup> The SVF contains ADSCs in addition to a variety of other components, including endothelial cells and progenitors, pericytes, smooth muscle cells, leukocytes, and erythrocytes.<sup>72</sup> After overnight culturing, ADSCs are isolated as the plastic-adherent population and removed from the other

cellular components. Utilizing this preparation, stem cell yield is higher from adipose tissue than bone marrow: 1 g of aspirated adipose tissue yields approximately  $3.5 \times 10^5$  to  $1 \times 10^6$  ADSCs vs 500 to  $5 \times 10^4$  of bone marrow-derived MSCs (BM-MSCs) isolated from 1 g of bone marrow aspirate.<sup>11</sup> These steps are outlined in Figure 2.

Of note, while the protocol described by Zuk et al is widely used in basic science investigation, this protocol and others that are used in the laboratory setting are not approved for use in humans by the Food and Drug Administration (FDA). Therefore, proprietary techniques have been developed to apply ADSCs in the clinical setting. For example, in 2010, Lipogems (Lipogems International, SpA, Milan, Italy) developed a technique to obtain microfragmented adipose tissue with an intact stromal vascular niche to isolate MSCs<sup>10,58</sup> (Figure 3).<sup>67</sup> This product became clinically available in 2013, and other manufacturers subsequently developed ADSC harvesting and processing technologies, such as AutoPose Restore (Arthrex, Naples, FL).

## Therapeutic Components of Adipose Tissue

Several large number of studies have been published in animal models outlining the various mechanisms by which ADSCs act on cell signaling.<sup>4,6,25,30,36,47</sup> ADSCs exhibit multipotent differentiation, rapid proliferation, and self-renewal properties.<sup>26</sup> They have been found to differentiate into endothelial cells and promote vascularization through vascular endothelial growth factor (VEGF),<sup>20,73</sup> and they exhibit potent immunomodulatory potential through both autocrine and paracrine mechanisms.<sup>32</sup> ADSCs induce the migration of fibroblasts and keratinocytes through Ki-67 expression and alpha-smooth

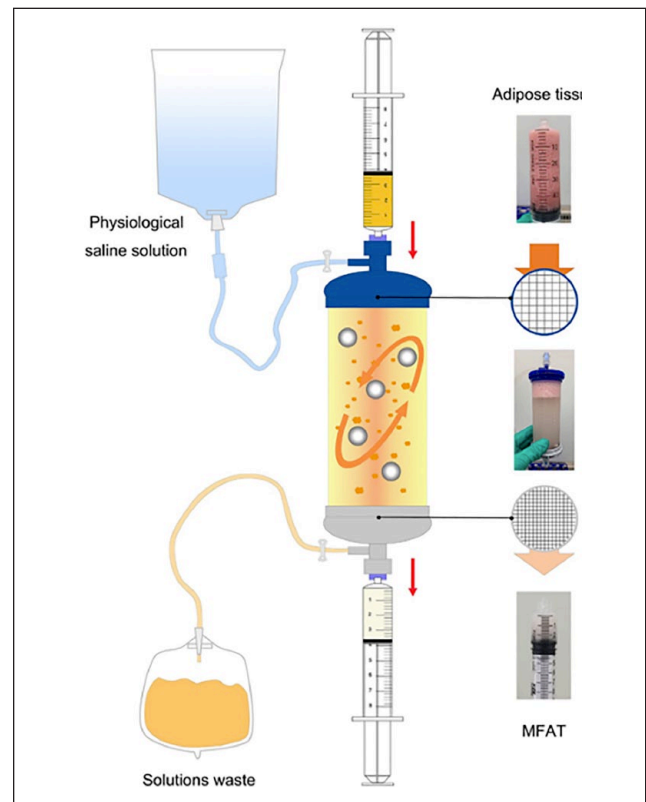


**Figure 2.** The processing methodology for adipose-derived mesenchymal stem cells. This process is not FDA-approved.

muscle alpha-actin ( $\alpha$ SMA) activation and can thus impact wound healing.<sup>3</sup> ADSCs have also been found to exhibit cartilage regenerative potential; specifically, the CD146+ subset has demonstrated the capacity for chondrogenic differentiation.<sup>34</sup> Importantly, *in vitro* studies have demonstrated that culture medium may impact chondrocyte differentiation of ADSCs. When cultured with growth factors such as insulin-like growth factor-1 (IGF-1), transforming growth factor-beta (TGF- $\beta$ ), or bone morphogenetic proteins (BMPs), ADSCs-derived chondrocytes exhibit the same type II collagen as mature chondrocytes.<sup>9,68</sup>

ADSCs also may impact bone deposition and growth. Bone modulatory potential is exhibited through the release of growth factors such as platelet-derived growth factor (PDGF), VEGF, and BMP-2.<sup>44</sup> ADSCs can also undergo osteogenic differentiation through major regulators such as Runx2 and Osterix (Sp7 transcription factor).<sup>29</sup> The Wnt signaling pathway serves as a regulatory factor between cellular lineages, guiding ADSCs away from adipogenic or chondrogenic lineage toward osteogenic lineages by increasing various signaling proteins.<sup>50</sup> Importantly, the mechanical environment in which ADSCs are placed will impact their osteogenic potential. For example, tensile strain through uniaxial or equiaxial stretching has been shown to increase Wnt signaling, favoring osteogenic cellular differentiation in ADSCs.<sup>52</sup> Thus, orthopaedists should recognize the contribution of the strain environment to the potency of ADSCs applied for various clinical use cases.

A recent study by Wang et al<sup>65</sup> demonstrated that adipose stem cells have a depot-dependent lineage preference. This rabbit study examined at subcutaneous adipose tissue (ScAT)– or infrapatellar fat pad (IPFP)–derived adipose stem cells. The authors concluded that ScAT- and IPFP-derived



**Figure 3.** Mechanism of the FDA-approved Lipogems® device. This process involves the original adipose tissue being pushed through the blue filter for the first cluster reduction. The core device is then aggressively shaken several times until the saline solution washes off the residual blood and oil. The second cluster reduction is then performed to obtain micro-fragmented adipose tissue via the extrusion of the inner adipose clusters into a syringe. Image courtesy of Xu et al.<sup>67</sup> Abbreviations: FDA, Food and Drug Administration; MFAT, micro-fragmented adipose tissue.

adipose stem cells of 4 donor-matched rabbits exhibited significant divergence in both proliferation and differentiation potential. Whereas the ScAT exhibited significantly higher proliferation and adipogenic capacity compared to donor-matched IPFP, stem cells from the IPFP displayed significantly higher chondrogenic potential in comparison to those from donor-matched ScAT. These results indicate that the harvest site of ADSCs is important, as different sites have different proliferation and differentiation potentials, which is an important consideration when determining the ideal harvest site.

### Applications in Foot and Ankle Surgery

Despite a relative paucity of investigations related to ADSCs in the foot and ankle, several studies have been published in the last decade. Herein, we will highlight the recent literature regarding the application of ADSC injections in various pathologic conditions of the foot and ankle and provide summation statements regarding the current evidence-based recommendation for ADSCs in each of the respective pathologies. These studies are also summarized in Table 1.

#### Plantar Fasciitis

One in 10 people will experience plantar fasciitis (PF) during their lifetime.<sup>59</sup> Risk factors for this condition include limited ankle dorsiflexion, increased body mass index, and standing for prolonged periods of time.<sup>18</sup> Patients commonly present with heel pain with their first steps in the morning.<sup>7</sup> Because of the lack of effective surgical options for this pathology, orthobiologics such as platelet-rich plasma (PRP) have been investigated for PF.<sup>23,23,69</sup> ADSC injection has been proposed as another therapeutic option in refractory cases.

A prospective, randomized, crossover pilot study by Gusenoff et al<sup>19</sup> evaluated the efficacy of perforating fat injections for chronic PF. Adults with plantar fascia thickening of  $\geq 4$  mm who failed standard treatment were included in this study. The intervention group (group 1), which received a fat injection and was then followed for 12 months, was composed of 9 female patients, and was followed for 12 months. Group 2 was composed of 4 female and 1 male patient, who were observed for 6 months, injected with a perforating fat infection, and then followed for 6 months. The fat in this study was hand-harvested from an unspecified donor site and processed using the Coleman technique. A total of  $2.6 \pm 1.6$  mL of fat was injected per foot at one of 2 sites. The authors used the Manchester Foot Pain and Disability Index (MFPDI) and American Orthopaedic Foot & Ankle Society (AOFAS) ankle-hind-foot scale scores to evaluate the clinical outcomes. In group 1, function and pain improved significantly as measured by

the MFPDI from  $7 \pm 2$  at screening to  $5 \pm 3$  at 6 months postoperatively to  $3 \pm 12$  at 12 months postoperatively. Pain also improved in this group significantly from  $12 \pm 4$  at screening to  $7 \pm 6$  at 6 months to  $5 \pm 5$  at 12 months. Both groups 1 and 2 had no significant change to the AOFAS scores at any time point.

Although the authors concluded that perforating fat injections for chronic plantar fasciitis demonstrated significant improvement in pain, function, and plantar fascia thickness, there are several causes for concern with this study. First, the authors stated that the fat was injected in each foot at one of 2 sites; however, they did not specify these sites, which could have important implications for treatment efficacy. This lack of standardization makes the interpretation of these results difficult. Furthermore, given the lack of a control group in this study, it is difficult to appraise the true efficacy of these injections.

#### Achilles Tendinopathy

Achilles tendinopathy (AT) is associated with overuse and is characterized by cumulative tissue microtrauma.<sup>63</sup> AT can be refractory to treatment given poor blood supply to the region,<sup>1</sup> but there has been significant recent advancement in treatment options for this pathology.<sup>62</sup> Accordingly, adipose-derived SVF has become a popular area of research for the treatment of AT.

A prospective randomized controlled trial (RCT) by Albano et al<sup>2</sup> assessed the correlation between MRI and ultrasonography findings and clinical outcomes after intra-tendinous injection of leukocyte-rich PRP or adipose-derived SVF in patients with noninsertional AT. This study included 43 patients with unilateral or bilateral noninsertional AT (58 tendons overall). Of these, 22 patients (28 tendons) were assigned to the PRP group, and 21 patients (30 tendons) were assigned to the adipose-derived SVF group. The adipose tissue was manually lipoaspirated from the patient's abdominal subcutaneous tissue by a plastic surgeon. The authors used the VAS scale as their outcome measure. The patients in the PRP group had a mean pretreatment VAS score of  $6.3 \pm 1.3$ , which decreased to  $1.9 \pm 1.4$  ( $P < .001$ ) at the 6-month follow-up. The patients in the adipose-derived SVF group had a mean pretreatment VAS of  $6.5 \pm 1.5$ , which decreased to  $1.6 \pm 1.9$  ( $P < .001$ ) at the 6-month follow-up. Furthermore, the adipose-derived SVF group had statistically significant increases in tendon thickness on both ultrasonography and MRI, whereas the PRP group did not. Despite a theoretical association between larger tendon size and worsening degeneration in AT, this larger tendon thickness correlated with improvements in VAS pain score. Conversely, the PRP group had statistically significant signal intensity on MRI, whereas the adipose-derived SVF group did not. However, it must be noted that this change in signal intensity for the PRP group was

**Table 1.** A Summary of the Studies That Have Been Published Within the Past Decade Regarding the Use of Adipose Injections in Pathologies of the Foot and Ankle.

Study	Pathology	Design	Number of Participants (Adipose-Derived Group)	Number of Participants (Control Group)	Outcome	Description of Results
Gusenoff et al <sup>19</sup> (2022)	PF	Prospective, randomized, crossover pilot study	9	5	Benefit	In group 1, function improved significantly on the MFPI from $7 \pm 2$ at screening to $5 \pm 3$ at 6 mo postoperatively to $3 \pm 2$ at 12 mo postoperatively. Pain also improved in this group significantly from $12 \pm 4$ at screening to $7 \pm 6$ at 6 mo to $5 \pm 5$ at 12 mo. Both groups 1 and 2 had no significant change to the AOFAS scores at any time point.
Albano et al <sup>2</sup> (2017)	AT	Prospective, randomized, controlled trial	21 (30 tendons)	22 (28 tendons)	Benefit	The patients in the PRP group had a mean pretreatment VAS of $6.3 \pm 1.3$ , which decreased to $1.9 \pm 1.4$ ( $P < .001$ ) at the 6-mo follow-up. The patients in the adipose-derived SVF group had a mean pretreatment VAS score of $6.5 \pm 1.5$ , which decreased to $1.6 \pm 1.9$ ( $P < .001$ ) at the 6-mo follow-up. Furthermore, the adipose-derived SVF group had statistically significant increases in tendon thickness on both ultrasonograph and MRI scans, whereas the PRP group did not. Conversely, the PRP group had statistically significant signal intensity on MRI, whereas the adipose-derived SVF group did not.
Uselli et al <sup>60</sup> (2018)	AT	Randomized, controlled clinical trial	21	23	Benefit	At the 15- and 30-d time points, the SVF group scored significantly better than the SVF group for the VAS, AOFAS, and VISA-A. However, there was no difference at 60, 120, and 180 d.
Kim et al <sup>27</sup> (2014)	OLT	Cohort study	24	26	Benefit	In the marrow stimulation group, the mean VAS score improved from $7.1 \pm 1.2$ to $3.9 \pm 0.8$ , the mean AOFAS score improved from $68.5 \pm 5.6$ to $78.3 \pm 4.9$ , and the mean Tegner score improved from $3.4 \pm 0.6$ to $3.5 \pm 0.8$ . In the MSC group, the mean VAS score improved from $7.1 \pm 0.8$ to $3.2 \pm 0.8$ , the mean AOFAS score improved from $67.7 \pm 4.7$ to $83.3 \pm 7.0$ and the mean Tegner score improved from $3.4 \pm 0.5$ to $3.9 \pm 0.7$ .

(continued)

Table 1. (continued)

Study	Pathology	Design	Number of Participants (Adipose-Derived Group)	Number of Participants (Control Group)	Outcome	Description of Results
Braille et al <sup>5</sup> (2021)	HR	Case report	1	0	Benefit	The patient's preoperative, 6-mo, and 9-mo follow-up AOFAS pain scores were all 30. His AOFAS function score preoperatively was 35, which improved to 40 at 6-mo follow-up and was also 40 at 9-mo follow-up. His VAS score was 7 at baseline and improved to 5 at 6-mo follow-up. At 9-mo follow-up, his VAS score was 0.
Natali et al <sup>41</sup> (2021)	Ankle OA	Prospective, open-label, uncontrolled pilot study	31	0	Benefit	The AOFAS scores at preoperation, 6-mo, 12-mo, and 24-mo follow-up were $56.4 \pm 17.52$ , $80.97 \pm 9.01$ , $84.17 \pm 12.23$ , and $66.5 \pm 15.71$ , respectively. The FADI scores at preoperation, 6-mo, 12-mo, and 24-mo follow-up were $59.47 \pm 16.99$ , $75.05 \pm 8.78$ , $82.0 \pm 11.39$ , and $71.83 \pm 10.88$ , respectively. The VAS scores at preoperation, 6-mo, 12-mo, and 24-mo follow-up were $7.03 \pm 0.95$ , $3.61 \pm 0.92$ , $3.26 \pm 0.63$ , and $4.35 \pm 1.25$ , respectively. All results for AOFAS, FADI, and VAS were statistically significant aside from the AOFAS score at 24-mo follow-up.
Shimozono et al <sup>53</sup> (2021)	Ankle OA	Retrospective cohort study	19	0	Benefit	At mean follow-up of 14.3 mo, both the FAOS for pain and quality of life significantly increased from 48.8 and 20.1 preoperatively to 61.1 and 30.1, respectively. The mean VAS score also significantly improved from 6.1 at baseline to 3.8 at final follow-up. Notably, however, more than a third of patients were unsatisfied with their outcomes.

Abbreviations: AOFAS, American Orthopaedic Foot & Ankle Society; AT, Achilles tendinopathy; FADI, Foot and Ankle Disability Index; FAOS, Foot and Ankle Outcome Score; HR, hallux rigidus; MSC, mesenchymal stem cells; MFPDI, Manchester Foot Pain and Disability Index; MRI, magnetic resonance imaging; OA, osteoarthritis; OLT, osteochondral lesions of the talus; PF, plantar fasciitis; PRP, platelet-rich plasma; SVF, stromal vascular fraction; VAS, visual analog scale; VISA-A, Victorian Institute of Sports Assessment–Achilles.

minimal. Furthermore, the data on PRP in general for AT are controversial, with many studies showing that it has no effect.<sup>42</sup> Thus, although the authors concluded that both PRP and adipose-derived SVF seemed to allow for clinical benefit, this finding is misleading, as the literature overwhelmingly does not support the use of PRP for the treatment of AT. Thus, the only conclusion that can be drawn is that ADSC is no more effective than PRP, which has not been shown to be superior at this point in time.

Another RCT by Usueli et al<sup>60</sup> concluded that intratendinous ADSC injections provide a safe and efficacious treatment for AT. This study included 44 patients, 23 of whom were assigned to a PRP group and 21 to the ADSC group. A small volume of adipose tissue (50mL) was manually lipoaspirated from the patient's abdominal subcutaneous tissue by a plastic surgeon. All patients were assessed preoperatively and at 15, 30, 60, 120, and 180 days after treatment using the VAS pain scale, Victorian Institute of Sport Assessment-Achilles (VISA-A), AOFAS, and SF-36 form. At the 15- and 30-day time points, the SVF group scored significantly better than the SVF group for the VAS, AOFAS, and VISA-A. However, there was no difference at 60, 120, and 180 days. The authors concluded that both treatments allowed for a significant improvement with respect to baseline.

### *Osteochondral Lesions of the Talus*

Because of the tenuous blood supply to the talus, some osteochondral lesions of the talus (OLTs) remain refractory to various therapeutic measures.<sup>31,48</sup> Thus, ADSCs have been proposed as an adjunct to encourage healing in OLTs.<sup>52</sup>

A cohort study by Kim et al<sup>27</sup> compared the clinical and MRI outcomes between injection of ADSC with marrow stimulation and marrow stimulation alone in patients with OLTs. A total of 49 patients (50 ankles) were included in this study. Of these ankles, 26 underwent marrow stimulation alone (conventional group), and 24 underwent marrow stimulation with an injection of SVF-containing MSCs (MSC group). Adipose tissue was harvested from the patient's buttock through tumescent liposuction. The authors assessed outcomes with the VAS pain scale, AOFAS score, Tegner activity scale, and the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score.

In the conventional group, the mean VAS score improved from  $7.1 \pm 1.2$  to  $3.9 \pm 0.8$ , the mean AOFAS score improved from  $68.5 \pm 5.6$  to  $78.3 \pm 4.9$ , and the mean Tegner score improved from  $3.4 \pm 0.6$  to  $3.5 \pm 0.8$ . In the MSC group, the mean VAS score improved from  $7.1 \pm 0.8$  to  $3.2 \pm 0.8$ , the mean AOFAS score improved from  $67.7 \pm 4.7$  to  $83.3 \pm 7.0$ , and the mean Tegner score improved from  $3.4 \pm 0.5$  to  $3.9 \pm 0.7$ . All clinical outcomes (VAS, AOFAS, and Tegner scores) improved significantly in the MSC group compared with the conventional group ( $P = .003$ ,  $P = .009$ , and  $P = .041$ , respectively).

There was also a significant difference in the mean MOCART score between the conventional and MSC groups, which is the scoring system the authors used to evaluate the MRI scans. The MOCART score is out of 100 and contains 9 variables, such as degree of repair and filling of the defect; integration to border zone; surface, structure, and signal intensity of the repair tissue; and presence of adhesions or effusion.<sup>38</sup> Among these 9 variables, there were significant differences between the groups in the degree of defect repair and filling of the defect and subchondral bone ( $P = .041$  and  $.038$ , respectively). The overall MOCART score in the conventional group was  $49.4 \pm 16.2$  compared to  $62.1 \pm 21.8$  in the MSC group ( $P = .037$ ). Furthermore, there were significant correlations of the MOCART score with all clinical outcome scores (VAS, AOFAS, and Tegner scores) in both groups ( $P < .05$ ). At this point in time, the clinical and MRI outcomes of injection with SVF containing ADSCs with marrow stimulation are too limited to support their use in OLTs.

### *Hallux Rigidus*

Hallux rigidus (HR) is a relatively common disorder that is present in 2.5% of people aged  $\geq 50$  years.<sup>21,46</sup> To our knowledge, there is only a single case report describing the use of ADSC injections for the treatment of HR.<sup>5</sup> The patient in this study was treated with an injection of ADSCs, which were obtained from the abdomen, and followed up after 9 months. Although this patient's AOFAS and VAS scores both improved at the final follow-up, no conclusions can be drawn as this is the only study to our knowledge that looks at the role of ADSC injections in the treatment of HR, and treatment efficacy cannot be determined from case reports.

### *Ankle Osteoarthritis*

Ankle OA is a debilitating condition that affects the daily life of nearly 250 million people worldwide.<sup>45</sup> The disease is associated with pain, dysfunction, and is a leading cause of disability, especially among the elderly population.<sup>24</sup>

A retrospective cohort study by Shimozone et al<sup>53</sup> evaluated the efficacy of intraarticular injections of autologous micronized adipose tissue with ankle arthroscopic debridement in patients with advanced-stage posttraumatic osteoarthritis (PTOA) of the ankle. This study included 19 patients (19 ankles) with Kellgren-Lawrence (KL) grades 3 and 4. Eighty to 120 mL of aspirated abdominal tissue was obtained via liposuction. This adipose tissue was then transferred from each Vaclock syringe to a single 60-mL syringe using a Luer-lock connector. The harvested fat was processed in the Lipogems processing kit according to the manufacturer's technique guide (Lipogems International, SpA). This step decreases the size of the adipose tissue clusters with a gentle mechanical action while simultaneously removing

oil and bloody residues from the mixture. The resulting microionized adipose tissue was then transferred into a few 10-mL syringes that were injected into the patient. The authors used the VAS and the Foot and Ankle Outcome Scores (FAOS) to evaluate the clinical efficacy of treatment. At a mean follow-up of 14.3 months, the mean FAOS for pain significantly increased from 48.8 preoperatively to 61.1 ( $P=.029$ ) and significantly increased from 20.1 preoperatively to 30.1 ( $P=.048$ ). The mean VAS score significantly improved from 6.1 to 3.8 at the final follow-up ( $P=.003$ ). A total of 10.5% (2/19) of patients were very satisfied, 31.6% (6/19) satisfied, 26.3% (5/19) neutral, 21.1% (4/19) unsatisfied, and 10.5% (2/19) very unsatisfied with their outcomes.

## Conclusion

ADSCs exhibit multipotent differentiation potential and are capable of the release of several growth factors and protein moieties that may impact regenerative potential in various therapeutic applications. Within foot and ankle surgery, ADSCs have been applied to PF, AT, OLT, HR, and ankle OA. Although case reports, case series, and some limited controlled trials have demonstrated the potential efficacy of ADSCs across these pathologies, further high-quality research is needed before ADSCs can be definitively recommended for foot and ankle applications.

## Ethical Approval Statement

No ethics approval was needed for this study. No patients were included in this work.

## Declaration of Conflicting Interests

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