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Efficacy and Duration of Intra-Articular Autologous Micro-Fragmented Adipose Tissue in Athletes with Ankle Osteoarthritis: A 36-Month Follow-Up Study

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Abstract: Introduction: The intra-articular injection of autologous micro-fragmented adipose tissue (MAT) is increasingly used to manage pain and dysfunction in subjects with osteoarthritis (OA). The purpose of this retrospective study was to report the safety and clinical outcomes of intra-articular MAT in athletes with ankle OA. Methods: Participants were 21 symptomatic athletes aged 18–30 years suffering from mild-to-moderate ankle OA, who received 7 mL autologous MAT after failure of six-month conservative treatment. Clinical evaluation was performed before the procedure and at 6, 12, 24, and 36 months using the visual analog scale for pain, the American Orthopedic Foot and Ankle Society score and the Foot and Ankle Disability Index score. Patient satisfaction was assessed at 36 months. Results: The clinical scores documented a significant or marked improvement throughout the follow-up ($p < 0.05$). However, at 36 months, they were significantly lower compared with the 24-month time point ($p < 0.05$), although they were still significantly better than the baseline scores. There were no intraoperative or postoperative complications. Altogether, 81% of patients were very satisfied and 19% were satisfied. Conclusions: Intra-articular MAT injection appears to be a safe and effective treatment for ankle OA. In particular, it offers athletes wishing a fast return to their sports a new, minimally invasive therapeutic option.

Keywords: osteoarthritis; adipose-derived mesenchymal stem cells; orthobiologics; retrospective study; sport

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1. Introduction

Osteoarthritis (OA) is a highly common condition that can affect any joint in the body. Its main features are articular degeneration, cartilage destruction, and inflammation [1]. Due to the increasing life expectancy, its incidence is expected to rise [2]. The prevalence of ankle AO is less than 1% of the adult population [3]. Rarely idiopathic, ankle AO is largely due to trauma [4,5]. The main risk factors for ankle AO include deformity, whether congenital or acquired, rheumatic disease, malleolar fracture, and ankle sprains sustained during sport activities. As a result, younger patients with high functional demands are affected more frequently [6–8]. Ankle OA adversely influences quality of life by impairing the activities of daily living. Athletes clearly experience even more severe limitations [9]. Current OA management guidelines differ in relation to patient age, functional demands, and disease severity. Conservative approaches include weight loss, orthotics, physical therapy, analgesics, non-steroidal anti-inflammatory drugs, and intra-articular injections of substances such as hyaluronic acid (viscosupplementation), corticosteroids, and platelet-rich plasma (PRP) [10,11].

In recent years, the interest in non-pharmacological therapies has been mounting, as a rising number of patients demand "natural" treatments. Orthobiologic treatment employs natural, i.e., biological substances to manage patients with orthopedic conditions.

These substances are derived from donors or, more often, from the patient's own tissues, and are used to help musculoskeletal lesions-such as bone fractures and muscle, tendon, and ligament lesions-to heal more rapidly [12]. The rationale for their effectiveness is the fact that they are applied at a higher concentration than naturally occurs in the body [13]. These substances include bone grafts, autologous blood, PRP, autologous conditioned serum, and stem cells.

Stem cells have the unique ability to reconstitute tissues where the presence of a high amount of dead or dying cells hampers regeneration. There are two main types of stem cells. Embryonal stem cells are found exclusively in the early stages of fetal development, whereas mesenchymal stem cells (MSCs) are found throughout life [14]. Key features of stem cells are their ability to self-renew and differentiate into multiple cell types [15].

Notably, stemness involves the ability to maintain the pool of stem cells and to genrate daughter cells capable of differentiating into specialized cells and tissues. MSCs can be isolated from a number of mesenchymal tissues such as bone marrow, synovial membrane, periosteum, and adipose tissue and can differentiate to cartilage as well as tendon and bone cells [15].

In recent years, a novel orthobiologic substance, micro-fragmented adipose tissue (MAT), has increasingly been used to foster tissue-healing in patients with knee and ankle OA [16,17]. MAT has been reported to have marked anti-inflammatory and regenerative properties both in vivo and in vitro; it is administered as an intra-articular injection and involves a very low rate of complications [18,19]. The Lipogems® system (Lipogems International S.p.a., Milano, Italy) is a class II medical device that is used to reduce the size of adipose tissue clusters [20]. It produces MAT by mechanical disaggregation of the lipoaspirate and by the separation and elimination of blood residues and pro-inflammatory oil. MAT is then rapidly injected into the painful joint. The effects of MAT include vascular stabilization and the inhibition of several macrophage functions that characterize the inflammation process of a wide range of orthopedic and dermatological conditions [21–23].

Although several studies have reported promising results in patients with OA treated with intra-articular MAT, additional information is required [24]. In particular, data on the outcomes of ankle OA treated with autologous MSCs derived from adipose tissue (ADSCs) are limited, especially where athletes are concerned [17].

To the best of our knowledge, there are no studies assessing clinical outcomes and patient satisfaction in athletes with ankle OA treated with MAT. Based on our experience with this system [22], we decided to test the hypothesis that the biological properties of MAT can improve treatment outcomes in young sport-practicing subjects with ankle OA.

The aim of this study was to examinate pain, functional outcomes, and complications in a cohort of athletes with ankle OA managed with the intra-articular injection of autologous MAT, who were followed-up for 36 months.

2. Materials and Methods

2.1. Design

This is simple retrospective design with one group [25], a single-center, pilot study for which ethics board approval was not required. All patients provided their informed consent to the use of their medical records and personal data at the time of admission. All procedures were in accordance with the institutional and national ethical standards of the institutional committee on human experimentation and with the Declaration of Helsinki as revised in 2014.

The records of all non-elite athletes with ankle OA who underwent the intra-articular injection of autologous MAT from January 2016 to November 2022 and had a follow-up of at least 36 months were retrieved from the institutional database. The following data were collected: demographics, body mass index (BMI), physical demands of the job

(light/heavy work), tobacco use, etiology of ankle OA, sport(s) practiced, American Society of Anesthesiologists (ASA) class, Kellgren–Lawrence (KL) stage. All adverse events were recorded.

2.2. Partecipants

The cohort included patients who had been diagnosed with ankle OA based on history, physical examination, and imaging findings, and had been managed conservatively. If, after 6 months of conservative treatment (physical therapy, intra-articular cortisone injections, rest, and anti-inflammatory drugs), they still reported significant pain, they were offered the intra-articular injection of autologous MAT.

Inclusion criteria were the following: patients aged 18–30 years who had ankle OA with a KL grade of I–II, a history of chronic ankle pain with limited daily activities for 6 months or longer, and/or failure of 6-month conservative treatment.

Exclusion criteria were the following: patients under 17 years old and over 31 years old, acute ankle trauma or ligament injury, rheumatic disease, septic arthritis or cutaneous infection involving the ankle, systemic cardiovascular disorders, current anticoagulant therapy, thrombocytopenia and/or coagulation disorders, degenerative joint deformities (KL grade III–IV), and intra-articular steroid or viscosupplementation injections performed within the last 3 months. Patients with abdominal infection, malignancy, pregnancy, a history of immunodeficiency, chronic oral corticosteroids or immunosuppressive therapy, a past or current history of malignant disorders, chemotherapy within the last 5 years, a diagnosis of transient ischemic attack in the last 6 months, and those who refused to sign the informed consent form were also excluded. The patients who were eligible after the application of these criteria were offered MAT treatment.

All procedures were performed by a single surgeon (V.I.).

2.3. Analysed Variables

Baseline data and postoperative functional outcomes were obtained from patients' medical records. The American Orthopedic Foot and Ankle Society (AOFAS) [26], Foot and Ankle Disability Index (FADI) [27], and Visual Analog Scale (VAS) [28] scores were collected before the procedure and at 6, 12, 24, and 36 months for the evaluation of quality of life, residual function and pain, respectively. Patient satisfaction was tested at 36 months.

2.4. Instruments Used for the Study and Procedure Followed

Participants were placed in supine position on a table in a dedicated room. Under aseptic and sterile conditions and local anesthesia, a small incision was made in the abdominal area, below the umbilicus, to insert a 17 G blunt cannula connected to a Luer lock syringe (60 cc).

Patients then received a percutaneous injection of 500 mL saline, 50 mL 2% lidocaine, and 1 mL (1:1000) epinephrine into the abdominal subcutaneous adipose tissue. After 10 min, adipose tissue (approximately 60 mL) was manually harvested using a 13 G blunt cannula connected to the syringe. The lipoaspirate was processed using the Lipogems® system according to the manufacturer's instructions [20]. The system includes a single-use device consisting of a transparent cylindrical container containing stainless steel balls. The device was filled with saline; after introducing the lipoaspirate, mechanical agitation was performed to fragment the fat.

The chamber was then flushed with saline to wash out impurities and 7 mL of the MAT product thus obtained was placed in a syringe. MAT was then promptly injected into the ankle under ultrasound guidance through an anteromedial approach using a 22 G needle. A gentle, passive range of motion exercises was performed immediately after the injection.

Patients were discharged from 2 to 3 h after the procedure with instructions for the following days. Full weight-bearing was initiated in hospital immediately after the procedure. Ankle mobilization and muscle strength exercises were started on the day of the

operation and continued for at least 2 weeks. Patients were recommended cold therapy and rest for at least 24 h. Mild activities and a gradual return to sports were allowed as tolerated. The fat donor site was medicated every 3 days. An abdominal binder was applied for 15 days, then the sutures were removed.

2.5. Statistical Analysis

Data were organized using Excel (Microsoft (Version 16.75.2), Redmond, WA, USA). Categorical variables were expressed as numbers and percentages, whereas continuous variables were expressed as mean and standard deviation (SD). The principal dependent variables of clinical outcomes were AOFAS, FADI and VAS scores. Student's tests were conducted for the evaluation of changes in preoperative and at 6, 12, 24 and 36 months of follow-up. Statistical analyses were performed using XLSTAT (Version 2021.2.2) resource pack (XLSTAT-Premium, Addinsoft Inc., New York, NY, USA). A p-value < 0.05 was considered significant.

3. Results

3.1. Patient Characteristics

According to the institutional database, 21 patients meeting the inclusion and exclusion criteria were treated at our department from January 2016 to November 2022. There were 16 men and 5 women, whose mean age was 23.9 years (±4.5). Their demographic and clinical details are reported in Table 1.

Table 1. Preoperative and perioperative patient demographics.

Variable	Patients
Number	21.0
Age, mean (SD) [range]	23.9 (4.5) [18.0–30.0]
Gender	
Male (%)	16.0 (76.2)
Female (%)	5.0 (23.8)
Side	
Right (%)	10.0 (47.6)
Left (%)	11.0 (52.4)
BMI (kg/m^2), mean (SD) [range]	26.0 (4.7) [20.5–37.9]
Physical demands of the job	
Light work (%)	13 (61.9)
Heavy work (%)	8.0 (38.1)
Tobacco use (%)	12.0 (57.1)
Etiology of OA	
Idiopathic (%)	4.0 (19.1)
Traumatic (%)	17.0 (80.9)
Sports	
Tennis (%)	3.0 (14.3)
Soccer (%)	7.0 (33.3)
Basketball (%)	2.0 (9.5)
Volleyball (%)	2.0 (9.5)
Jogging (%)	2.0 (9.5)
Other sports (%)	5.0 (23.8)
ASA class	
1 (%)	14.0 (66.7)
2 (%)	7.0 (33.3)
Radiographic stage (Kellgren–Lawrence)	
Grade I	11.0 (52.4)
Grade II	10.0 (47.6)

SD: standard deviation; BMI: body mass index; ASA: American Society of Anesthesiology.

3.2. Functional Outcomes, Patient Satisfaction and Complications

The VAS, AOFAS, and FADI scores collected before the procedure and at 6, 12, 24 and 36 months were analyzed with Student's test. The analyses demonstrated a significant or marked improvement in all scores throughout the study period. The VAS and FADI scores showed significant differences with the baseline scores at all time points (all $p < 0.005$). The AOFAS scores were also significantly different from the baseline score at 6, 12, 24, and 36 months ($p = 0.013$, $p < 0.005$, and $p < 0.005$, and $p < 0.005$, respectively). All these data are reported in Table 2.

Pairwise comparisons were also performed, between 6 and 12 months, 12 and 24 months, and 24 and 36 months (Table 2). The differences in the VAS, AOFAS, and FADI scores between 6 and 12 months were not significant ($p = 0.760$, $p = 0.210$, and $p = 0.490$, respectively). In contrast, the differences between 12 and 24 months were significant for the AOFAS and FADI scores ($p < 0.005$ and $p = 0.006$, respectively), but not for the VAS score ($p < 0.090$). Finally, all scores significantly declined between 24 and 36 months for the VAS, AOFAS, and FADI scores ($p < 0.005$, $p = 0.040$ and $p = 0.020$, respectively).

Table 2. Postoperative functional tests and patient satisfaction.

Variable	Values		*p*-Value
VAS			
Baseline, mean (SD) [range]	6.9 (1.0) [5.0–9.0]	Baseline vs. 6 months	<0.005
6 months, mean (SD) [range]	3.7 (1.1) [2.0–5.0]	Baseline vs. 12 months	<0.005
12 months, mean (SD) [range]	3.6 (0.9) [2.0–5.0]	Baseline vs. 24 months	<0.005
24 months, mean (SD) [range]	3.1 (0.6) [2.0–4.0]	Baseline vs. 36 months	<0.005
36 months, mean (SD) [range]	4.2 (1.2) [2.0–6.0]	6 months vs. 12 months	0.760
		12 months vs. 24 months	0.090
		24 months vs. 36 months	<0.005
AOFAS			
Baseline, mean (SD) [range]	53.1 (7.4) [42.0–65.0]	Baseline vs. 6 months	0.013
6 months, mean (SD) [range]	59.1 (7.5) [48.0–71.0]	Baseline vs. 12 months	<0.005
12 months, mean (SD) [range]	62.1 (7.6) [52.0–75.0]	Baseline vs. 24 months	<0.005
24 months, mean (SD) [range]	71.1 (7.5) [62.0–83.0]	Baseline vs. 36 months	<0.005
36 months, mean (SD) [range]	66.1 (7.6) [56.0–78.0]	6 months vs. 12 months	0.210
		12 months vs. 24 months	<0.005
		24 months vs. 36 months	0.040
FADI			
Baseline, mean (SD) [range]	56.7 (17.0) [30.0–90.0]	Baseline vs. 6 months	<0.005
6 months, mean (SD) [range]	70.7 (10.4) [45.0–90.0]	Baseline vs. 12 months	<0.005
12 months, mean (SD) [range]	73.0 (10.7) [47.0–93.0]	Baseline vs. 24 months	<0.005
24 months, mean (SD) [range]	82.3 (10.3) [55.0–95.0]	Baseline vs. 36 months	<0.005
36 months, mean (SD) [range]	75.3 (8.6) [58.0–90.0]	6 months vs. 12 months	0.490
		12 months vs. 24 months	0.006
		24 months vs. 36 months	0.020
Satisfaction questionnaire, 36 months:			
Very satisfied (%)		17.0 (81.0)	
Satisfied (%)		4.0 (19.0)	

SD: standard deviation; VAS: Visual Analog Scale; AOFAS: American Orthopedic Foot and Ankle Society Scale; FADI: Foot and Ankle. Disability Index. PRE: preoperative.

The trends in the AOFAS and FADI scores during the 36 months of follow-up are shown in Figure 1.

At 36 months, 81% of patients were very satisfied and 19% were satisfied (Table 2). None of the patients experienced complications related to the injection either during the procedure or in the follow-up period.

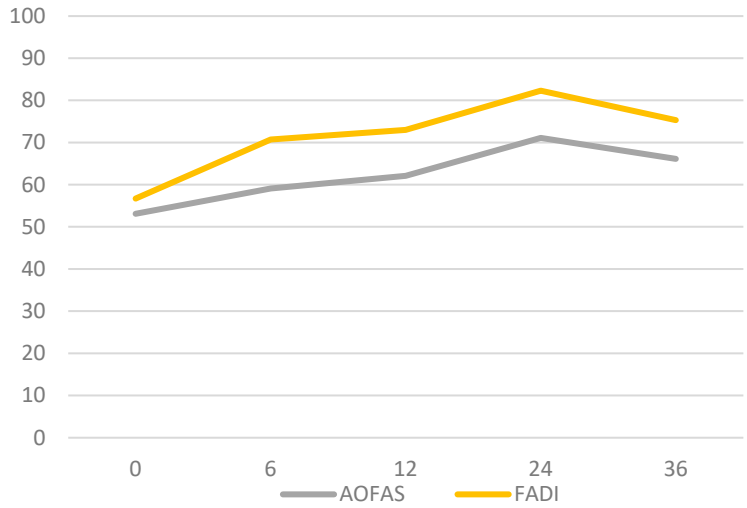

Figure 1. AOFAS and FADI scores at 36 months follow-up.

4. Discussion

Our study was undertaken to assess the safety and efficacy of intra-articular autologous MAT in treating symptomatic non-elite athletes with ankle OA who were experiencing limitations in the activities of daily living and/or had been managed by a conservative approach. Although several works have evaluated the effectiveness of intra-articular MAT in treating ankle pain [17,29,30], to the best of our knowledge, none have examined its efficacy in athletes. In a recent study, the effect of autologous MAT on ankle OA was examined after arthroscopic debridement; the authors reported that the procedure was safe and that it had favorable effects on patients with advanced ankle OA, even though they stressed that the procedure may be more effective in patients with moderate OA [30]. The most important finding of our work is that autologous MAT proved to be a useful approach to treat pain, inflammation and associated dysfunction in athletes with mild-to-moderate ankle OA. Clinical evaluation documented a significant or marked improvement in the clinical scores throughout the three-year follow-up period. Although the clinical measures showed that the benefits peaked at two years and the scores subsequently declined during the third year, the difference with the baseline scores was still significant. None of the patients experienced complications related to the procedure.

According to a review [31] and a systematic review of the literature [32], treatment with autologous MAT is safe in patients with orthopedic conditions and usually has favorable clinical outcomes. The rationale of the effects of autologous MAT injection is well-documented. Its actions depend on paracrine effectors contained in the adipose tissue, which possess anti-inflammatory and pro-regenerative properties [33,34]. These chemical mediators support cell viability and proliferation, as well as extracellular matrix deposition, by downregulating the markers of inflammation and matrix degradation in several cell types, including cartilage cells and synoviocytes [35]. In vivo, MAT has been documented to exert a chondroprotective action in a rabbit OA model by enhancing the repair of cartilage defects [36,37]. In fact, both in vitro and in vivo studies have reported that stem cells are characterized by anti-inflammatory and regenerative properties through growth factors and cytokines [38]. Therefore, autologous MAT may provide an ideal approach to treat ankle OA in younger patients, especially athletes, even enabling surgical procedures to be postponed.

Our data indicate that the treatment was increasingly effective up to 24 months, and that its benefits gradually declined over the final 12 months, similar to viscosupplementation [23]. A possible explanation for this decline is joint overuse by the athlete [39]. Nonetheless, the benefits accruing over the first 24 months are a clear indication of treatment success, and the subsequent worsening of clinical scores did not involve their return to baseline.

5. Conclusions

In conclusion, the intra-articular injection of MAT is a safe and effective treatment for athletes with ankle OA, offering a practical and minimally invasive therapeutic option to patients who wish to return to their previous level of sport performance and are ineligible for surgical procedures. These preliminary results are intriguing and warrant further and more extensive investigation to identify which patients would benefit most from MAT treatment, suggesting to the clinician how best to design a treatment plan for these patients.

The present study has a number of limitations. They include the lack of a formal placebo or a control group treated with corticosteroid injection and assessed at the same time points. Moreover, the results were not analyzed on the basis of age, BMI, or OA severity. Finally, the postoperative period did not include the monitoring of patient activities to prevent problems such as joint overuse.

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