Review Article

Journal of Clinical Cases

Adipose Tissue Stem Cells For Knee Arthritis And Cartilage Lesions: A 3 Years Follow-up

Dimitrios Tsoukas[*1], Christos Simos[1] and Vasilliki Kalodimou[2]

[1]Orthopaedic Clinic for Advanced Arthroscopic Sports and Regenerative Medicine MITERA Hospital Athens, Greece

[2]Cytometry-Research and Regenerative Medicine IASO Maternity and Research Hospital Athens Greece

[*]**Corresponding author:**
Dimitrios Tsoukas,
Sports and Regenerative Orthopaedic Surgeon, Director Orthopaedic Clinic for Advanced Arthroscopic Sports and Regenerative Medicine Mitera Hospital Athens Greece,
Email: www.info@tsoukas-ortho.gr

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1. Abstract

1.1. Introduction:
The purpose of this research article is to evaluate the efficacy and the safety of injections of stromal vascular fraction SVF, obtained with mini-lipoaspiration of fat tissue for knee osteoarthritis and cartilage lesions.

1.2. Materials and Methods:
A total of 76 patients (45 females and 31 males, mean age 64 years old and range 53-75 years old, BMI no more than 30%, with symptomatic primary osteoarthritis of the knee, without previous arthroscopic intervention) underwent during the period January 2018 to February 2021 a local tumescent lipoaspiration procedure of 60-80 cc of fat tissue from the abdomen. SVF was obtained after centrifugation according the Adiprep Adipose Transfer System by Harvest-Terumo, Plymouth, MA, USA technique. The final product was checked with flow cytometry for absolute numbers, vitality and CDs population. It was injected intraarticularly into the patients knees that were divided in two groups: Group -1 had patients with knee osteoarthritis Kellgren- Lawrence grade early 4 and Group-2 with osteoarthritis K-L grade 2-3. IKCD and KOOS questionnaires were used to evaluate clinical effects and measure patient's subjective assessment of pain, joint mobility, and physical disability before the injections. They were repeated at 6 months, one, two and three years post injections. Knee cartilage lesions patients were divided in two subgroups: Group-A (11 patients with OA K-L grade 2-3 and Outterbridge cartilage lesions grade 2-3) and Group-B (7 patients with OA K-L grade early 4 and cartilage lesions Outterbridge grade late 3 -early 4) were estimated with quantitively analysis of MRI at 1, 2 and 3 years post-injections.

1.3. Results:
The average IKDC score in Group-1 was 45.9, 63.2, 62.4, 60 and 52. The KOOS score of the same group was 53, 79, 72, 69 and 62 at the end of the third year. The average total IKDC score in Group-2 was at baseline 48.3, at 6months 78.2, at one year 77, at two years 70.4 and at three years 61 and the KOOS score of this group was accordingly 57, 84, 86, 79 and 69 at three years. For the patients with cartilage lesions Group-A presented lesser volume mean numbers of the lesion 74% at the end of the first year post-injection, 61% at the second and 52% at the end of the third year at 2 out of 7 patients of the group. The rest of them had no significant difference. Lesser volume mean number of the lesions on Group-B was 85-88%, 70% and 61% at the end of the third year at 5 out of 11 patients of the group. The rest of them had no significant difference.

1.4. Conclusion:
Adipose derived SVF injected intraarticularly in arthritic knees seems to provide good to excellent clinical results for 3 years and radiological results for cartilage lesions for 2 years post-injections. All patients were satisfied with this treatment with reduction in pain and better joint mobility, especially after 2-3 months up to 3 years. No serious side effects or complications reported.

2. Keywords:
Stromal Vascular Fraction; SVF; Adipose tissue; Adipose stromal stem cells; Osteoarthritis; Knee, Regenerative medicine

3. Introduction

A challenge to the orthopaedic surgeon in the 21st century is the desire of the ageing patient to remain physically and mentally active and to continue to contribute to society. In osteoarthritis, degenerative joint disease results from breakdown of joint cartilage and underlying bone [1]. Among the over 60, about 10% of males and 18% of females are affected [2, 3], and osteoarthritis causes significant disability [4, 5]. Conventional conservative treatments which include non-steroidal anti-inflammatory drugs, glucosamine, chondroitin sulphate, omega-3 fatty acids, hyaluronic acid, and corticosteroid injections, showed limited clinical benefits [6–8], without preventing the progression of knee osteoarthritis (KOA) or providing long-term improvements in function and joint pain [9]. When KOA progresses to the final stages and non-surgical treatments fail, total knee replacement may be an effective alternative [10, 11]. Considerable benefits have resulted from the biomechanical solutions of the past 50 years, with better biomaterials and implants for joint replacements, more precise instrumentation and computer-aided navigation techniques.

However, implants have a finite lifespan owing to loosening or other modes of failure and may require further surgery involving increased

morbidity for the patient, with 20% of patients presenting with persistent pain or loss of function at 12 months [12–14]. With the recent increase in interest for regenerative medicine, patients often undergo intra-articular orthobiologic therapy for KOA and cartilage disease [15, 16]. . Autologous chondrocytes implantation (ACI) could be one approach to regenerate an articular cartilage defect. Nowadays, small cartilage defects can be repaired using this technique, although its effectiveness is still controversial. Preparation of chondrocytes for ACI is associated with several limitations, which include the limited number of chondrocytic cells and their dedifferentiation during the culture period for propagation. For this reason, an alternative cell source should be found. Mesenchymal stem cells (MSCs) are another alternative that can be used to regenerate articular cartilage defects. Mesenchymal stem cells (MSCs) obtained from autologous bone marrow cells (BMAC) or from adipose- derived stromal cells (ADSCs) included in stromal vascular fraction (SVF) [17–20], which is a functionally diverse population of cells that is believed to be synergistic and able to communicate with other cells in their local environment and platelet-rich plasma (PRP) obtained from autologous blood are used for these purpose [21]. MSCs are multipotent cells that show strong self-renewal capabilities, they are characterised by cell surface markers, with a differentiation ability to form chondrocytes, adipocytes, and osteocytes [22]. MSCs may differentiate and participate in the regeneration of connective tissues, given their capability to home in on and attach to diseased tissue [23–25], including bone, articular cartilage, tendon, ligament and fat [22, 26–29]. Furthermore, BMAC and ADSCs exest anti-inflammatory, angiogenic, trophic, and immunomodulatory effects which can retard the progression of OA [30–32].

Adipose Derived Benefits & Composition

- Easy to harvest cells.
- Obtained in larger volume, at lower risk, less painful, less intrusive and easier to extract than bone marrow.
- 50 - 1000 times more stem cells than bone marrow
- MSCs are contained within a multi-potent cell pool termed the Stromal Vascular Fraction (SVF),

Although this area of research holds infinite promise, it is also influenced by scientific, ethical, moral and political controversies.

4. Materials and Method

4.1. Study design:

Between January 2018 and February 2021 ,76 patients (45 females and 31 males, mean age 64 years old and range 53-75 years) underwent a minor belly lipoaspiration and knee intra-articular injection of ADSCs obtained according the Adiprep Adipose Transfer System by Harvest-Terumo, Plymouth, MA, USA. Ethical and regulatory considerations were followed as described before.[1]

The patients' age, sex, body mass index (BMI), previous surgery on the affected knee, and medical comorbidities were recorded at pre-operative assessment. Selection criteria were clinical findings of knee osteoarthritis with radiographic evidence of degenerative joint disease on standing radiographies. Exclusion criteria were age over 75 years, Kellgren-Lawrence grade 0 and 1, body mass index more than 30, more than 10° varus or valgus deformity, and infectious or inflammatory joint disease [2]. Patients were divided in two groups: Group-1 with osteoarthritis K-L grade early 4 and Group -2 with knee osteoarthritis Kellgren- Lawrence grade 2 to 3. IKCD and KOOS questionnaires were used to evaluate clinical effects and measure patient's subjective assessment of pain, joint mobility, and physical disability before the injections. They were repeated at 6 months, one, two and three years post injections.

Knee cartilage lesions patients were devided in two subgroups Group-A (11 patients with OA K-L grade 2-3 and Outterbridge cartilage lesions grade 2-3) and Group-B (7 patients with OA K-L grade early 4 and cartilage lesions Outterbridge grade late 3 -early 4) were estimated with quantitively analysis of MRI at 1, 2 and 3 years post-injections. For the belly lipoaspiration we first induce under light sedation 60 ml of tumescent fluid through two tiny holes from both sides of the belly. Figure 1

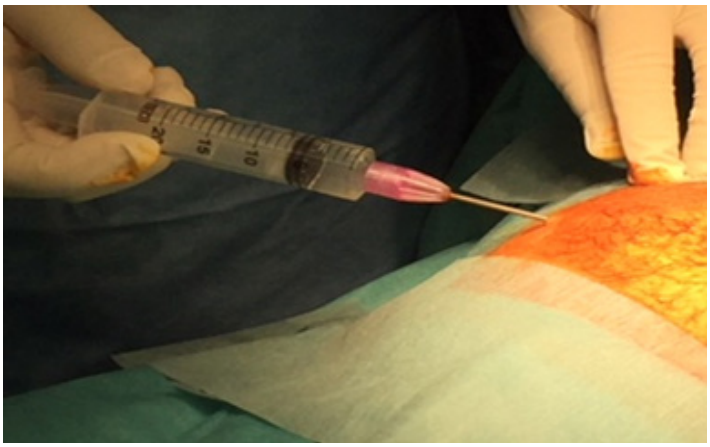

Figure 1: Tumuscent fluid injection under light sedation

Minor belly lipoaspiration obtaining 60ml of adipose tissue: After application of vacuum, the physician is free to move the harvesting cannula in a forward and back series of passages. It is important that these passages are within the same plane and of the same pattern used during the placement of tumescent solution Figure 2

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Figure 2: Minor lipoaspiration

The desire to produce the best compact grafts with minimal remaining fluid excess has led us to include use of optimal centrifugation (1000 g for 3–4 minutes) to effectively compress the graft materials, help to more precisely separate fluid from harvested graft, and facilitate removal of the unwanted free lipid component. Figure 3

Figure 3: Graft centrifugation at the SmartPRep®2 APC+ ™centrifuge

After centrifugation we have the concentrated fat in our syringe. Figure 4

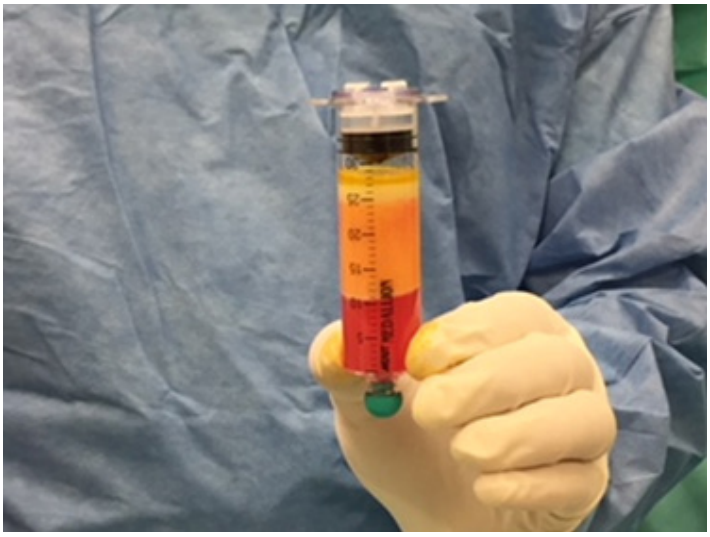

Figure 4: At the top we have oil and lipid fraction (yellow) , then we have the lipid barrier , then the concentrated adipose tissue (orange) and at the bottom excess fluid.

It is really crucial the removal of excess infranatant fluid and of oils and lipids. Residual oils, lipids and cellular debris may induce a serious inflammatory reaction. Tissue SVF contains the total adipose tissue microenvironment with a variety of cells like adipocytes, pre-adipocytes and mesenchymal stem cells and also structural matrix for cell viability and proliferation. Figure 5

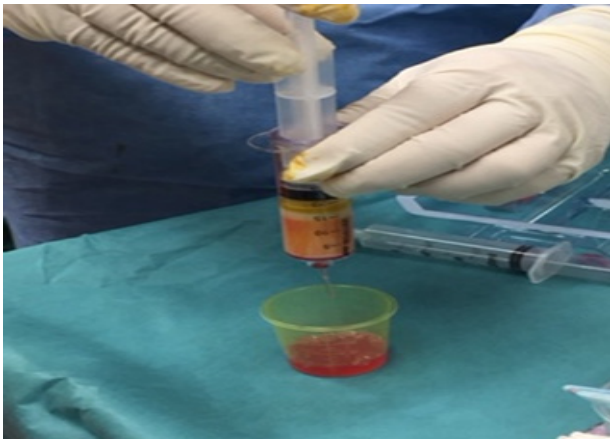

Figure 5: Removal of excess fluid, oils, lipids and cellular debris.

The final product is been transfered to smaller syringes and injected into the knee by lateral suprapatellar approach with the leg extended. Figure 6a and Figure 6b All the procedures were performed by the same senior Orthopaedic Surgeon DT even the lipoaspirates.

Figure 6a: Transfer of the final product in smaller syringes

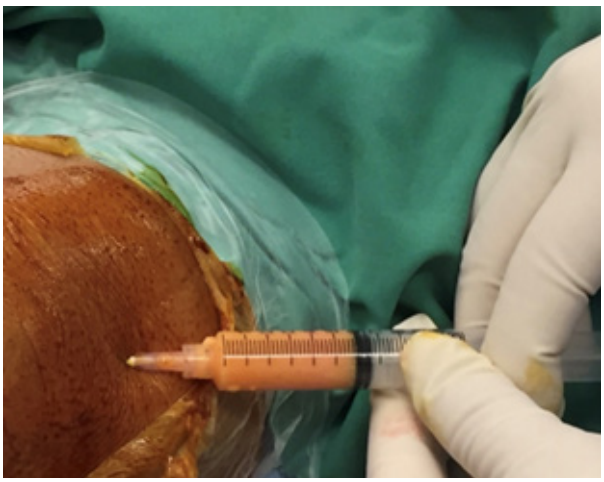

Figure 6b: Knee intraarticular injection by lateral suprapatellar approach.

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4.2. Flow cytometry studies

For flow cytometry, the cells were cultured in six well plates in complete DMEM media to 80% confuency. These were harvested using mild trypsin EDTA and washed with PBS. We found:

- 660000 absolute numbers
- CD35, CD45, CD271, CD29, CD90, CD73, CD105, CD44, CD14,CD31, CD166CD133
- Vitality 87%

4.3. Statistical analysis

Formal power calculations were not performed. Two tailed statistical analyses were performed and confidence intervals are presented with 95% degree of confidence. All statistical tests used a signifcance level of $\alpha \leq 0.0$

5. Results

5.1. Osteoarthritis

The results of the Questionnaires IKDC and KOOS were:

KL EARLY 4

BEFORE INJECTION	
IKDC SCORE 45.9	KOOS SCORE 53
6 MONTHS	
IKDC SCORE 63,2	KOOS SCORE 79
1 YEAR	
IKDC SCORE 62,4	KOOS SCORE 72
2 YEAR	
IKDC SCORE 60.5	KOOS SCORE 69
3 YEAR	
IKDC SCORE 52	KOOS SCORE 62

KL 2-3

BEFORE INJECTION	
IKDC SCORE 48,3	KOOS SCORE 57
6 MONTHS	
IKDC SCORE 78,2	KOOS SCORE 84
1 YEAR	
IKDC SCORE 77	KOOS SCORE 86
2 YEAR	
IKDC SCORE 70.4	KOOS SCORE 79
3 YEAR	
IKDC SCORE 51	KOOS SCORE 69

Both treatment groups demonstrated significant improvement from pre- to post-procedure in KOOS and IKDC scores with highest scores achieved at 6 months and at the end of the first year. The average total IKDC score in Group-1 was 45.9 before injection, 63.2 at 6 months post-injection 62.4 at the end of the first year, 60.5 at the end of the second year and 52 at the end of the third year. The KOOS score of the same group was accordingly 53, 79, 72, 69 and finally 62 at the end of the third year Group-2 was at baseline IKDC score 48.3, at 6months post-injection 78.2, at one year 77, at two years 70.4 and at the end of three years 61. KOOS score of this group was accordingly 57, 84, 86, 79 and 69 at three years.

5.2. Cartilage Lesions

The results of the mean volume numbers of the cartilage lesions measured with quantitively analysis of MRI at 1, 2 and 3 years post-injections were:

5.3. Outterbridge Early 4 Cartilage Lesion

All measurements were made by one senior radiologist without any knowledge of the study protocol: he estimated lesser volume mean numbers of osteochondral lesion 74% at the end of the first year post-injection, 61% at the end of the second year and 52% at the end of the third year. at 2 out of 7 patients. The rest had no significant difference, We noticed clinical worsening of their symptoms at the end of the second year.

5.4. Outterbridge 2-3 Cartilage Lesion

Lesser volume mean numbers of osteochondral lesion 85%-88% at the end of the first post- injection year (Figure 7 and Figure 8). 70% at the end of the second year and 61% at the end of the third year at 5 out of 11 patients. The rest had no significant difference. We noticed clinical worsening of their symptoms at the end of the third year.

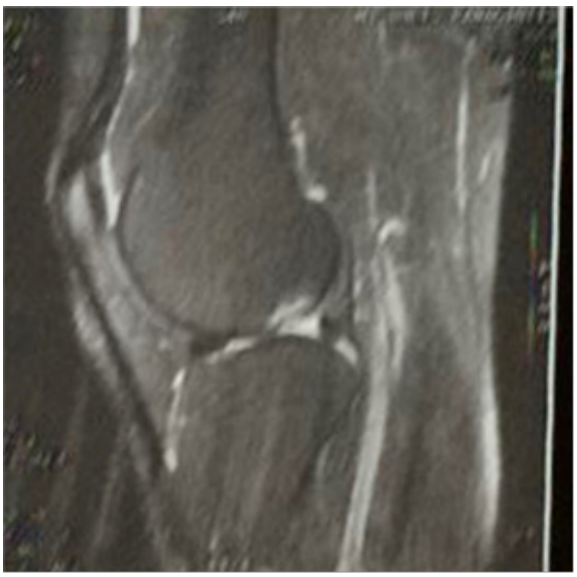

Figure 7: Chondral lesion Outterbridge 3 with subchondral bone bruise medial femoral condyle.

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Figure 8: Same knee, 1 year post injection complete healing of cartilage lesion without subchondral bone bruise.

6. Conclusion-Discussion

Based on the findings of this study, knee intra-articular SVF injections improve clinical and functional scores in patients with symptomatic osteoarthritis at 6 months of post-injection follow-up till almost the end of the third year. Patients with osteoarthritis KL staged early 4 and with cartilage lesion Outterbridge 3-4 have earlier worsening of their symptoms. Patients with osteoarthritis staged KL 2-3 treated with ADSCs injections have better clinical and functional results than patients with severe osteoarthritis staged KL early 4. Intra-articular adipose derived MSCs for knee osteoarthritis improve pain and function for 24 - 36 months, with evidence of improvement in cartilage status in focal rather in diffuse cartilage lesions. Conversely, a recent meta-analysis of 13 RCTs showed that intra-articular MSC injection was not superior to placebo in pain relief and minimum clinically important functional improvement for patients with symptomatic KOA [47]. In MRI evaluations of cartilage repair, current evidence showed controversial results, with no improvement in cartilage status [49–51]. An accurate pre- and postoperative planning with MRI imaging must be obtained to evaluate the improvement of cartilage status [52]. This study has some limitations. The choice of treatment was not randomized and there was no comparison with other therapies, such as placebo or other injection such as hyaluronic acid, PRP or BMAC .

6.1. Ongoing Researches And New Perspectives

There are unfortunately many factors, which can heavily interfere with Regeneration and cell integration into the recipient site. New lines of research in order to improve the regenerative response are mandatory (53). The redirection of cytokines pools into a probiotic pathway, the stimulation of MUSE cells population through a specific donor site preparation and delayed harvesting phase , Bioactive Composite Therapies in Orthopaedic Surgery [54] PhotoBio Modulation, extraction and concentration of autologous and allogenic Exosomes and exertional gene expression are important pillars of our new strategies destinated to further expand the clinical applications and outcomes.

Pioneers in regenerative therapies application and in those ongoing studies, are plastic and orthopaedic surgeons. Many orthopaedic surgeons have been trained to perform lipoaspiration by plastic surgeons. On the other hand plastic surgeons showed us [54], that Orthopedic Surgery is definitely the surgical specialty that most can benefit of these new therapeutic strategies At the present time the use of basic and advanced regenerative procedures in Orthopedic Surgery is estimated close to 30% of the total number of procedures globally performed (3 times more than in Plastic Surgery). A close collaboration between the two specialties can offer a lot in regenerative medicine applications.

7. Acknowledgment

The present study followed the principles of express in the Declaration of Helsinki and received ethic approval by the Ethical Committee of the MITERA Hospital Athens, Greece. All patients signed written consent to participate to the study.

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