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ORIGINAL PAPER

# Treatment of knee osteoarthritis by intra-articular injection of concentrated autologous adipose tissue: a twenty four month follow-up study

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## Abstract

**Purpose** To evaluate the safety and efficacy of autologous concentrated adipose tissue for the treatment of knee OA.

**Methods** Eighty-seven patients with knee arthritis from grade 1 to 3, according to Kellgren-Lawrence scale, have been treated with knee arthroscopy and successive intra-articular injection of concentrated adipose tissue. The efficacy of the treatment has been evaluated by the Knee Society Score, Lysholm Score, Forgotten Joint Score, Knee Injury and Osteoarthritis Outcome Score and Noise Reporting Scale.

**Results** A total of 78/87 patients concluded the study. Overall, the patients were satisfied with the intervention and a significant reduction of the pain was observed in 67 patients, while the others did not report any change in pain severity or worsening. A statistically significant improvement was observed in the considered orthopaedic index, and no major adverse effects were described. The first week after the intervention, most patients reported knee swelling. Five patients failed because they underwent knee replacement surgery between five and nine months from treatment.

**Conclusions** In patients with knee OA, a single intra-articular injection of autologous adipose tissue reduced knee pain, stiffness, improved knee function and quality of life without severe complications.

**Keywords** Knee · Arthritis · Concentrated autologous adipose tissue · Mesenchymal stem cells

## Introduction

Osteoarthritis (OA) is the most common chronic joint disease characterized by cartilage destruction, inflammation and degeneration of the joint, and it is expected to increase over time [1]. Knee OA is one of the main causes of disability among adults, leading to pain, stiffness and decreased function of the joint. The standard pattern of non-pharmacological treatment of knee OA includes weight reduction and lifestyle modifications [2, 3]. Injections of hyaluronic acid, corticosteroids and local anaesthetic represent additional but not definitive options for the early stages of the joint degeneration [4, 5]. Various treatment options have been proposed for localized chondral lesions [4, 6]. The major challenge remains the treatment of diffuse chondropathy.

The treatment for end stage and severe arthritis is the total knee arthroplasty (TKA) [5, 7, 8]. Among the large number of treatment possibilities for knee OA, the novel approach of regenerative medicine is an area of growing interest especially in the challenging subset of younger patients, who have high functional demands yet limited indications for invasive surgical treatments. Nevertheless, they could also have application for elder suffering patients, who cannot afford a TKA. Nowadays, the issue has even extended to middle-aged active patients who increasingly expect to maintain a high activity level and postpone or avoid metal resurfacing. Recent improvements in regenerative medicine introduced cellular

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treatments based on intra-articular injection of minimally manipulated adipose tissue in the clinical practice. Different methods allow to obtain minimally manipulated adipose tissue, for instance Coleman technique [9] or medical devices which can provide microfragmented autologous fat tissue (μFAT) [10] or purified microfiltered adipose tissue [11]. Adipose tissue is a rich source of naturally occurring regenerative cells, such as mesenchymal stem cells (MSCs), which show properties of self-renewal, multi-lineage differentiation and immunomodulatory capacity, and can activate and influence the microenvironment by secreting different growth factors and cytokines [9, 12, 13]. Although treatment of knee OA with adipose tissue has been suggested as safe and effective [14–16], concerns still exist about the correct procedure, the evaluation of the results and the mechanism of action; thus, accurate studies are still needed.

The aim of this study was to evaluate the safety and efficacy of autologous concentrated adipose tissue, derived from lipoaspirates processed with different methods, for the treatment of knee OA.

## Materials and methods

### Patient selection

Between July 2016 and July 2019, 87 patients with a symptomatic arthritic knee have been treated with knee arthroscopy and successive intra-articular injection of concentrated adipose tissue. Nine patients have been lost to follow-up: one patient died while eight patients did not complete the questionnaires for the follow-up evaluation. Therefore, the results of the study included 78/87 patients: 43/78 were women and 35/78 men; mean age was 59.5 ± ten years and mean BMI was 25.3 ± 3.8 kg/m$^2$. The average follow-up has been 23.5 months.

Inclusion criteria were men and women affected by knee arthritis from grade 1 to 3, according to Kellgren-Lawrence (K-L) scale for the radiological evaluation of arthritis, who underwent knee arthroscopy, with BMI > 20 kg/m$^2$, with normal renal and coagulation functions. Exclusion criteria were patients under corticosteroid treatment, intra-articular injection of hyaluronic acid in the previous two months, patients presenting with a grade 4 arthritis according to Kellgren-Lawrence scale, BMI > 29 kg/m$^2$ and comorbidities such as rheumatoid arthritis and diabetes.

### Outcomes and clinical evaluation

The primary outcome of this publication was to evaluate the functional and pain improvement after the procedure.

Patients have been evaluated before surgery and at follow-up through clinical questionnaires: new Knee Society Score (KSS), Lysholm Score, Forgotten Joint Score (FJS), Knee Injury and Osteoarthritis Outcome Score (KOOS). Noise Reporting Scale (NRS) has been used to evaluate pain walking and climbing stairs. In addition, patients have been interviewed about their return to the previous sport activity. At last, the presence of clinical complications such as infections, reactions, inflammations and immune responses has been studied.

### Surgical technique

Patients underwent a hyperbaric subarachnoid anaesthesia using temporary Trendelemburg position to reach the periumbilical area, and intraoperative antibiotic prophylaxis with a second-generation cephalosporin. The procedure started with subcutaneous abdominal liposuction, then with knee arthroscopy and the procedure was completed with intra-articular injection of adipose tissue. All patients were discharged in the first post-operative day. Weight-bearing was not allowed for ten days and the patients were discouraged to mobilize the knee for ten days post-operatively according to previous reports [17–19]. In this period, isometric exercises for the quadriceps were allowed; then, patients were subjected to physiotherapy to recover full articulation of the joint, muscular tone and the correct gait pattern.

### Preparation of concentrated adipose tissue for infusion

The abdomen has been chosen as the source of adipose tissue. A saline solution containing adrenaline (devoid of lidocaine in order to preserve the cell viability) was injected in the subcutaneous adipose tissue; after 30 minutes, the liposuction was performed until the harvesting of approximately an average of 180 mL of adipose tissue [20]. The lipoaspirates of 33 patients were processed through centrifugation, according to Coleman technique. Briefly, lipoaspirates were centrifuged at 3000 rpm for three minutes to collect fat phase and discard oily and hematic phases [21]. The lipoaspirates of 27 patients were treated with Lipogems®, a medical device which requires shaking of the harvested adipose tissue into the processing cylinder provided with several steel spheres, whose action emulsified, and microfractured the adipose tissue. Then, a minimal enzyme-free manipulation in a sealed sterile device gradually reduced the adipose clusters allowing also to discard the oily and hematic residues. At the end of the whole procedure, an extract of μFAT was obtained [22]. The lipoaspirates of 24 patients were treated with Lipocell®, another device which allows to insert fat in a semipermeable membrane commonly used for dialysis purposes, where it is dialyzed with a filter and washed with 300–500 mL of saline solution. Then, gentle brushing was done on the outside of the bag to facilitate the washing, to obtain lipoaspirates cleared from blood, and the flowing washing solution was transparent. At the end of

the whole procedure, an extract of microfiltered adipose tissue was obtained [11].

## Statistical analysis

GraphPad Prism 8.0 has been used; two-way ANOVA has been performed to analyse differences among the groups with Bonferroni's multiple comparison test. Differences have been considered significant for $p < 0.05$. Means and standard deviations (SD) were used to estimate central tendency and variability.

## Compliance with ethical standards

Patients gave their consent; the study was authorized by the local Institutional Revision Board (IRB) in accordance with the ethical standards (N.Registro CER 068REG2017). The work has not been published before in any language, is not being considered for publication elsewhere and has been read and approved by all authors. Each author contributed significantly to one or more aspects of the study. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

# Results

Nine patients have been lost to follow-up: one patient died while eight patients did not complete the questionnaires for the follow-up evaluation. Therefore, the results of the study included 78/87 patients.

Patients have been asked about their degree of satisfaction with the intervention, based on a score going from 0 to 10. Overall, the patients were satisfied with the intervention and the consequent improvement in knee pain and function: mean degree of satisfaction was 6.86 ± 2.73 (range 0–10); 57 patients stated they would undergo the treatment again, 17 said they would not and four patients were uncertain about it.

Significant improvement in pain was observed in 67/78 patients: all of them reported a significant reduction in NRS score, both in walking and stairs climbing: NRS walking pre-surgery was 7.06 ± 1.96 (95% CI: 6.6–7.5) and post 2.38 ± 2.92 (95% CI: 1.7–3), while NRS climbing stairs pre-surgery was 7.24 ± 1.76 and post 2.87 ± 3. Despite general reduction of the pain, 16/78 (20.5% of the patients) reported a NRS score equal or superior to 6 after the intervention, 5/78 reported a worsening and 6/78 did not report any change in pain severity. Lysholm score improved from 60.3 ± 13.8 (range 40–99; 95% CI: 57.2–63.5) before the treatment to 84.5 ± 15.6 (range 40–100; 95% CI: 81–88) after surgery. The forgotten joint score FJS improved from 45.7 ± 18.1 (range 3–100; 95% CI: 41.6–49.8) to 77.6 ± 20.1 (range 28–100; 95% CI: 73.1–82.1) after surgery. Overall, a statistically significant improvement was observed in all the questionnaires answered by patients. KOOS and KSS showed an improvement in all their subscales (Table 1, Fig. 1 and Table S1).

There has been a general improvement in running: a consistent part of the patients reported having started running again, 8/78 patients noticed no change in running ability and only 1/78 patient declared a decreased running capacity. Concerning the daily life activity, most part of the patients had an improvement in the function of kneeling (Table 2). We also investigated whether the different types of lipoaspirate procedures could interfere with the outcomes, but we did not report any significant differences among the three different methodologies, as shown in Fig. 2.

**Table 1** KOOS and KSS pre- and post-treatment. Knee Injury and Osteoarthritis Outcome Score (KOOS) mean values ± SD before (PRE) and after (POST) the intervention. Knee Society Score (KSS) mean values ± SD before and after intervention. Delta between pre- and post-treatment was included along with the percentage of improvement for the specific outcome measures

| | Pre | Range | Post | Range | Delta pre-post (% improvement) | *p* value |
|---|---|---|---|---|---|---|
| KOOS mean values before and after treatment | | | | | | |
| Symptoms | 46.2 ± 16.5 | 22–100 | 78.3 ± 21.9 | 28–100 | 32.1 (59%) | 0.0001 |
| Pain | 41.1 ± 14 | 22–100 | 75.7 ± 14.5 | 22–100 | 34.6 (54%) | 0.0001 |
| ADL | 45.8 ± 14.5 | 15–100 | 79.5 ± 22.3 | 22–100 | 33.7 (57.6%) | 0.0001 |
| Sport | 18 ± 19.4 | 0–100 | 55.6 ± 34.1 | 0–100 | 37.6 (32.4%) | 0.0001 |
| QoL | 40.9 ± 14.6 | 19–100 | 72.5 ± 25.5 | 25–100 | 31.6 (56.4%) | 0.0001 |
| KSS mean values before and after treatment | | | | | | |
| Symptoms | 16.9 ± 3.9 | 4–24 | 9 ± 4.5 | 0–23 | − 7.9 (53.2%) | 0.0001 |
| Patient satisfaction | 15.9 ± 7.1 | 0–36 | 27.6 ± 10.3 | 0–40 | 11.7 (57.6%) | 0.0001 |
| Patient expectation | 13.5 ± 3.1 | 6–15 | 9.4 ± 3.7 | 3–15 | − 4.2 (69.6%) | 0.0001 |
| Functional activities | 48.8 ± 15.6 | 16–99 | 76 ± 22.9 | 21–100 | 27.2 (64.2%) | 0.0001 |

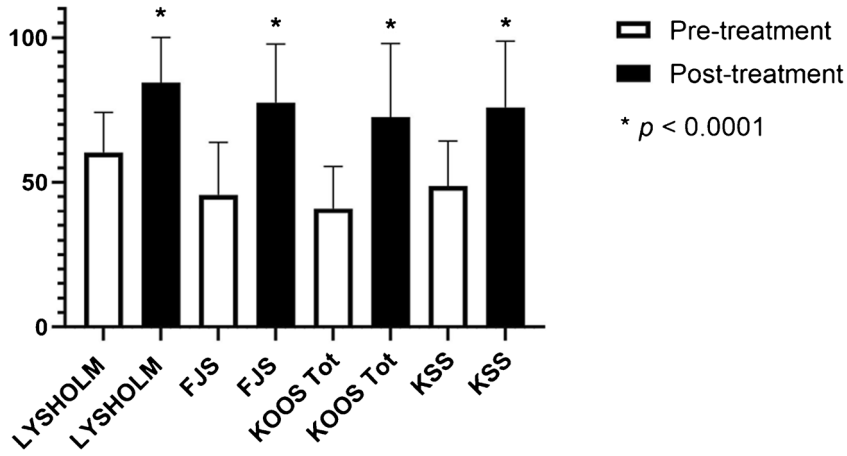


**Fig. 1** Orthopaedic Scores utilized to evaluate the efficacy of the treatment. All the examined scores show an improvement after concentrated adipose tissue treatment. Knee Society Score (KSS), Forgotten Joint Score (FJS), Knee Injury and Osteoarthritis Outcome Score (KOOS)

## Complications

No major adverse effects were described, such as massive deep venous thrombosis, neurovascular complications or infections. In the first week after the intervention, most patients reported knee swelling, which disappeared within six weeks. No cases of adverse, allergic or immune reactions at knee level have been observed. Furthermore, there were not registered adverse events related to the treatment. There were two cases of minor venous thrombosis and one delayed wound healing, which have been treated successfully with heparin and antibiotics, respectively.

## Failures

Concerning the failures, among the 78 patients who participated to the final follow-up, four patients underwent total knee replacement surgery between five and nine months from treatment. Another patient underwent uni-compartmental knee replacement 18 months after the treatment. The characteristics of the patients with a failure are shown in Table 3.

**Table 2** Patients sport activities before and after intervention. This table shows the number and the percentage of patients who referred mild, moderate, intense activity before (Pre) the intervention or were not able to do their own activity, and the number of patients who after (Post) the intervention recovered light, moderate or intense activity or have never recovered it. The number of patients unable to do sports reduced and the recovering of activities were evident after treatment

| | Pre | | | Post | | |
|---|---|---|---|---|---|---|
| | *M* | *F* | TOT | *M* | *F* | TOT |
| No activity | 10 | 24 | 34 (43.5%) | 2 | 11 | 13 (16.6%) |
| Soft activity | 19 | 17 | 36 (46.1%) | 11 | 16 | 27 (34.6%) |
| Moderate activity | 4 | 1 | 5 (6.4%) | 7 | 1 | 8 (10.2%) |
| Intense activity | 2 | 1 | 3 (3.8%) | 15 | 15 | 30 (38.4%) |

## Discussion

Clinical trials based on intra-articular injection of minimally manipulated autologous adipose tissue in OA joints reported improvement in pain, function and cartilage volume [9, 23, 24], due to the ability of autologous adipose tissue in releasing paracrine mediators able to counteract inflammation and reducing pain [14, 15]. In this study, we confirmed that intra-articular administration of concentrated adipose tissue was safe for treating knee OA, leading to a general improvement of the clinical symptoms, according to previous comparable reports [15, 25]. Indeed, we reported that a large majority (78%) of the patients expressed satisfaction and improvements with respect to knee function and/or pain, and 66% of the patients considered the procedure excellent (NRS < 2). A percentage of 20.5% of patients showed an improvement of NRS score after the treatment. Most patients did not practice any or soft sport activity before the treatment due to pain and stiffness, while after the treatment most of them were once again able to practice intense activities and sport, such as running and skiing. The return to sport is a parameter of great impact on the general satisfaction of patients about the intervention, indeed 57 of them would undergo this procedure again, 17 would not and four were uncertain about it. Only five patients reported a worsening in NRS score, and these patients were those with arthritis grade 3 in two compartments, severely symptomatic and widely informed about the possibility of failure. Therefore, this result suggests that the treatment cannot avoid TKA in case of knee affected by advanced severe arthritis.

Adipose tissue infusion was not associated with any adverse event including chondro-toxicity, allergies or implant rejection. We found in several cases a mild knee swelling associated with pain which disappeared in the first weeks after surgery according to previously published data [26]. The positive effect in terms of reduction of pain and increased motility of the joint can, at least partially, be ascribed to some protective molecules contained in MSCs secretome [27]. Indeed,

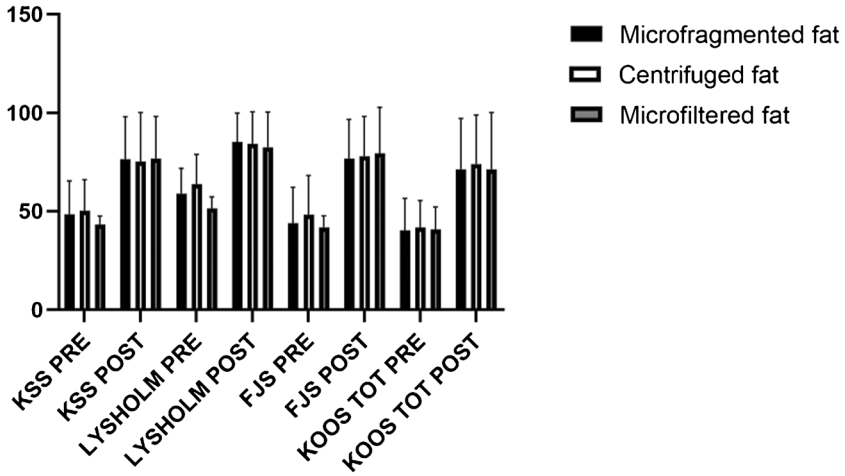


**Fig. 2** Different procedures to recover concentrated adipose tissue. Lipoaspirates were processed through 3 different methods to isolate adipose tissue for the intra-articular injection. The different types of lipoaspirate processing did not interfere with outcomes. Indeed, the scores resulted improved after treatment, compared to the pre-treatment ones, but scores were not significant different among the 3 types of processing of lipoaspirates. Knee Society Score (KSS), Forgotten Joint Score (FJS), Knee Injury and Osteoarthritis Outcome Score (KOOS)

MSCs secrete biological mediators that increase angiogenesis and cell proliferation, and have anti-inflammatory and immunomodulatory properties promoting tissue healing. A recent systematic review found that MSC infiltrations for knee OA can represent a feasible option, leading to an overall remarkable improvement of all clinical and functional outcomes with an extremely low complication rate. Patients treated at earlier-degeneration stages reported statistically significant improvements of VAS, WOMAC and walking distance [28].

MSCs can be utilized after ex vivo expansion, but also as bone marrow or adipose tissue infusion, because these tissues are enriched of MSCs. Since adipose tissue contains a higher amount of MSCs than bone marrow and concentrated adipose tissue can be directly obtained both in the operating room and in an outpatient procedure room by orthopaedic surgeons, through a minimal manipulation, many medical devices have been developed to release an adipose tissue extract ready to use. The advantage to use medical devices is that they are commercially available, and they consist in sterile, closed systems, preserving the sample from potential contaminations. In this work, we used three different methodologies to process lipoaspirates; thus, we also evaluated whether the different procedure to obtain adipose tissue for infusion can affect the results of the treatment, but we did not register any statistical differences among the different preparation methods. Overall percutaneous injection of adipose tissue following knee arthroscopy increased significantly clinical and functional scores in patients with early knee OA at a mid-term follow-up, confirming previously published data using the KOOS, IKDC-subjective, Tegner Lysholm Knee and VAS pain scales taken pre-operatively and at 12- and 36-month follow-up [15].

This study has some inherent limitations. First, it is a retrospective study, the follow-up is relatively short due to the novelty of the procedure, the number of patients is limited and there is not placebo and blinding of the treatment. The patients' samples were processed through three different methods, limiting the number of patients for each system. For future research, we will plan a blind and randomized study with placebo and a comparison of patients with and without surgical treatment. Furthermore, the Osteoarthritis Grade was

**Table 3** Characteristic of failed patients. Noise reported scale (NRS) shows high value of noise for these patients, both for walking and walking up the stairs. The types of complications are reported

| | Sex | Age | BMI | NRS walk pre | NRS stairs pre | NRS walk post | NRS stairs post | ADL level pre | OA degree | Complications |
|---|---|---|---|---|---|---|---|---|---|---|
| Patient 1 | F | 75 | 24.8 | 9 | 9 | 9 | 9 | No activity | III | Pain persistence |
| Patient 2 | M | 64 | 27.7 | 7 | 7 | 9 | 9 | No activity | III | Pain worsening |
| Patient 3 | M | 57 | 24 | 7 | 7 | 7 | 7 | Soft activity | II | Pain persistence |
| Patient 4 | F | 74 | 25 | 9 | 9 | | | No activity | III | Persistence of limitations in ADL |
| Patient 5 | M | 57 | 27.8 | 9 | 9 | 9 | 9 | No activity | II | Pain persistence |

*BMI* bone mass index, *ADL* activities of daily living, *NRS* Noise Reporting Scale

not verified by a blind reviewer. Besides, a direct or indirect description of the status of the cartilage and of the synovia is missing because magnetic resonance was not performed, due to budget restrictions. Informative and optimal examination, such as the biopsy and the histological evaluation are clearly not always applicable. Indeed, we previously published results on patients treated with adipose tissue [9], but the major part of data deriving from histological analysis concern infusion of MSCs, which showed efficacy in repairing cartilage lesions [29]. The associated arthroscopic surgical procedure may be questionable since some authors reported that arthroscopy is not useful for patients with degenerative meniscal tears and underlying degenerative arthritis. Indeed, Cattaneo et al. [25] studied the role of Lipogems in the same population, treated or not by surgical procedure, reporting better outcomes in patients without meniscectomy. Nevertheless, according to our preliminary data, the arthroscopy of the knee seems to be useful to reduce the concentrate of inflammatory synovial fluid which has a negative effect of MSC adhesion and function ([30] and personal unpublished results) and to rule out associated lesions which could cause persistent pain independent from a pure cartilaginous degenerative disease (e.g. meniscal fractures, loose bodies, synovial plication).

A relevant issue regarding this procedure is its regulatory aspect; indeed, FDA and European Medicinal Agency compliance must be considered for the use of the various commercially available devices for knee osteoarthritis. Lipogems and Lipocell are CE approved and Lipogems is also FDA approved. In Italy, the procedure for the treatment of the osteoarthritis using adipose extract either prepared using the standard Coleman procedure [21, 31] or with medical devices is cleared by the Centro Nazionale Trapianti since July 2015. On this topic, either European Medicinal Agency or Istituto Superiore della Sanità did not make any definitive statement on the subject.

## Conclusions

The main finding of this study was that a single intra-articular injection of autologous adipose tissue in patients with knee OA, K-L grade 1 to 3, reduced knee pain and stiffness and improved all the KOOS, new KSS, Lysholm and FJS clinical scores; patients gained an improved knee function and experienced a better quality of life both in daily activities and in sports without severe complications.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00264-020-04923-0.

**Authors' Contributions** Each author contributed significantly to one or more aspects of the study. The work has not been published before in any language, is not being considered for publication elsewhere and has been read and approved by all authors.

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**Data availability** The data reported are original and comply with the requested standard of accessibility.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This study was performed in line with the principles of the Declaration of Helsinki. The study was authorized by the local Institutional Revision Board (IRB) in accordance with the ethical standards (N.Registro CER 068REG2017).

**Consent to participate/publish** Informed consent was obtained from patients to participate at the study and to publish the relative data.

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