Intra-articular Injection of Autologous Fat Graft for the Treatment of Knee Osteoarthritis

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Abstract: Background: Knee osteoarthritis is a common degenerative joint disease which leads to major morbidity, disability, and health care utilization. It usually presents with arthralgia and stiffness of the joint. The aim of this prospective interventional study was to examine the therapeutic effects of intra-articular micro-graft injection of autologous fat for knee osteoarthritis. **Methods**: This study was conducted at King Abdulaziz University Hospital from January 2012 to October 2015; eighty adult patients (148 knee joints) were enrolled in this study. Patients were suffering from moderate to severe knee osteoarthritis. The majority of patients were having bilateral knee osteoarthritis (n= 68, 85.00%), then right knee (n= 9, 11.25%) and left knee (n= 3, 3.75%). Liposuction was performed to collect the fat micro-graft, then 10-20 ml of the prepared autologous fat micro-graft were injected intra-articular into the affected knee/s. **Results**: Visual analogue scale values of the joints' pain showed improvement after the fat injection compared to before, both during rest and with activity. The Western Ontario and McMaster Universities Osteoarthritis Index also indicated improvement, both in the three domains (pain, stiffness and physical function) and in total. **Conclusions**: The use of intra-articular autologous fat micro-graft is a safe, simple and effective new line of treatment for degenerative knee osteoarthritis. Longitudinal study is needed for follow up of these cases. **Clinical Question/Level of Evidence:** Therapeutic Studies –Level II.
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1. Introduction:

Chronic osteoarthritis is a major health problem affecting millions of people, especially the middle aged and elderly due to degenerative changes which cause pain, swelling, stiffness and a limitation of joint mobility. Treatment of osteoarthritis aimed to decrease pain, improve joint function and slow the disease progression. Treatment begins with patient education in self-management by modification of lifestyle and loss of weight. Pharmacological symptomatic therapies such as analgesics have limited effect with potentially serious side effects. Other treatment modalities including intra-articular injection of corticosteroids, viscous supplementation injections of hyaluronic acidwhich improve pain and viscosity, but these treatment had short improvement effect, costly and have a minimal risk of acute synovitis.[1-6] Recently, the intra-articular injection of platelet-rich plasma to human osteoarthritic and autologous adipose-derived mesenchymal stem cell (MSC) into dogs osteoarthritic showed encouraging results of improvement of the clinical symptoms and signs and joints functions.[7-9]

In current practice patients who have lost their joint cartilage and failed medical management are advised to have joint replacement with the associated disadvantages: it is a major procedure with complications, long hospitalization, absence from work and high cost.[10,11]Many studies have been performed focusing on the treatment options offered by stem cells, though this necessitates the process of isolation and processing of the stem cells.[12-15] In our previous work, we reported that injection of fat micro-graft directly into the animal and human joints without the use of any processing technique is safe and effective technique.[16,17]

The aim of this study was to confirm our previous preliminary result regarding the safety and efficacy of injecting fat micro-graft intra-articularly in 80 adult patients (148 knee joints) with chronic osteoarthritis.

2. Patients and Method:

This prospective interventional study was conducted at King Abdulaziz University Hospital Jeddah, Kingdom of Saudi Arabia from June 2012 to December 2015 after approval from the Local Research and Ethics Committee, No. 822-12 according to the latest revision of the *Declarationof Helsinki*. Eighty adult patients of both genders were screened for eligibility to participate in the study. Each patient underwent a complete medical history, a physical examination and full assessment of the joint. Informed written consent was obtained from each patient before treatment. All cases of severe to moderate knee osteoarthritis changes, confirmed by bilateral anterior - posterior standing and lateral supine radiographs involving one or both knees, were included in the study. Exclusion criteria were: recent knee surgery; chronic opioid intake; bleeding disorders; malignant disease; congenital or traumatic deformity of the knee joint and refusal of the patient to be included in the study.

The visual analogue scale for pain assessment (on scale 0-10 cm line, 0 = no pain and 10 = worst imaginable pain) was explained to patients during the preoperative visit; visual analogue scale at rest and during activity was obtained. The Western Ontario and McMaster Universities Osteoarthritis Index is a questionnaire widely used to assess the symptoms and physical disability associated with osteoarthritis. In this study we used 5 points Likert type Western Ontario and McMaster Universities Osteoarthritis Index to collect information regarding the 3 subscales of Western Ontario and McMaster Universities Osteoarthritis Index. Pain while (5 items): sitting or lying; walking; using stairs; standing; in bed. Stiffness (2 items): after first walking and later in the day. Physical Function (17 items): standing; walking; sitting; rising from sitting; stair use; bending; putting on or taking off socks; lying in bed; rising from bed; getting in or out of the bath; sitting on or rising from the toilet; getting in or out of a car; shopping; light household duties; heavy household duties.

Anesthesia and surgical interventions were explained to the patients. A list of adverse effects was reviewed with the patients to allow for reporting of any that may arise post-procedure. The procedures were performed under local anesthesia and sedation. Dexmedetomidine 0.7 mcg/kg/hr was administered intravenously as a sedative and pain reliever. Patients were monitored for heart rate, pulse oximetry, temperature and non-invasive blood pressure. The surgical site of liposuction was carefully chosen based on the availability of fat and the patients' wishes. Liposuction was performed under complete aseptic technique and antibiotic coverage of cefuroxime 1.5 gm IV one dose, one hr preoperative followed by 500 mg orally every 12 hrs for 5 days. Fat harvesting was obtained using ten-holes, Olivaire blunt cannula (Pouret Medical, Clichy, France) with 1 mm tip attached to a 10-ml Luer-Lok syringe (Terumo, Auburn, WA, USA). 30 mL of fat was collected and then left for 30 min to settle and separate into various layers, the upper and lower layers were removed while the middle layer of fat was kept for intra-articular injection (Figure 1). The surgical site was prepared and injected with 100 to 200 mL of tumescent solution. Solution was prepared by mixing 30 to 50 mL of 1% lidocaine, 0.5 mg (0.5 mL) of epinephrine in 449.5 mL of lactated ringers. The osteoarthritic knee joint was injected with autologous fat micro-graft intra-articular 15 to 20 ml through the lateral approach according to the case in an amount that did not produce high pressure inside the joint and did not pain to the patients due to tension of the joint capsule. All patients were followed up in the clinic on a regular basis every three months to assess incidence of side effects, complications, pain evaluation, stiffness and knee functions, and recurrence of pain.

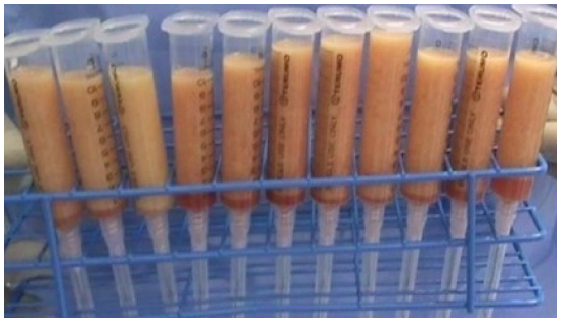

Fig. 1. Autologous Fat micrograftaspirate.

Statistical Analysis:

IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY USA) was used for data analysis. Data were presented as mean ± SD and minimum - maximum or number and percentage (n, %) as appropriate. Wilcoxon test for non-parametric variables was used to compare pre-injection to post-injection values. A probability of $P< 0.05$ was considered statistically significant.

3. Results:

Table 1 shows the demographic data and the clinical characteristics of the patients. The female patients numbered more than the males (72.50% versus 27.50%). Only 4 patients (5.00%) smoked and 1 (1.30%) was a previous smoker. The associated comorbidities were obesity (62.60%), hypertension (31.30%), type 2 *diabetes mellitus* (17.50%), hypothyroidism (12.50%), rheumatoid arthritis (10.00%), low back pain (7.50%), lower limb edema (1.30%) and hepatitis (1.30%).

Table 1. Demographic and clinical characteristics of patients.

Parameters	**Data** (number = 80)
Age (years)	61.81 ± 10.76 (38-85)
Weight (kg)	87.95 ± 15.12 (56-156)
Height (meter)	1.58 ± 0.10 (1.44-1.86)
Body mass index (kg/m^2)	34.98 ± 5.52 (23.01-50.60)
Gender	
Male	22 (27.50%)
Female	58 (72.50%)
Smoking	
Yes	4 (5.00%)
No	75 (93.75%)
Previous smoking	1 (1.25%)
Comorbidity	
Obesity	50 (62.50%)
Hypertension	25 (31.25%)
Type 2 diabetes mellitus	14 (17.50%)
Hypothyroidism	10 (12.50%)
Rheumatoid arthritis	8 (10.00%)
Low back pain	6 (7.50%)
Lower limb edema	1 (1.25%)
Hepatitis	1 (1.25%)

Data are expressed as mean ± SD (minimum-maximum) or number (%) as appropriate.

The period of osteoarthritis disease ranged between 1 and 33 years. The affected knees were mostly bilateral (85.00%), then right knee (11.20%) and left knee (3.80%). The medications used were mostly non-steroidal anti-inflammatory drugs (98.80%) then glucosamine (15.00%), prednisone (11.30%), methotrexate (7.50%) and relaxon (2.50%). Of the patients, 95.00% were treated by single fat injection while 1.30% received two fat injections and 3.70% received three fat injection treatments (Table 2).

Visual analogue scale values were significantly higher in pre- versus post-injection both during rest (7.37±1.85 versus 0.66±0.64, P=0.0001) and with activity (9.11±1.32 versus 1.31±0.79, P=0.0001), which reflected a marked improvement in osteoarthritis pain (Table 3).

Table 4 presented The Western Ontario and McMaster Universities Osteoarthritis Index before and after the intra-articular fat micro-graft injection. Great improvement was seen across all three domains (pain, stiffness and physical function) in the post intra-articular fat injection period compared to the pre-injection values (P=0.0001 for all measured parameters). The Western Ontario and McMaster Universities Osteoarthritis Index test total score also showed great improvement in the post intra-articular fat injection period compared to the pre-injection values (12.10±6.26 versus 81.09±9.87, P=0.0001; 12.60±6.52 versus 84.47±10.28, P=0.0001, respectively). The clinical improvement was considered on each patient overall and not on each individual joint.

Table 2. Disease duration and treatment of patients.

Parameters	**Data** (Number = 80)
Disease duration (years)	8.86 ± 6.85 (1-33)
Side of affected knee	
Right knee	9 (11.25%)
Left knee	3 (3.75%)
Bilateral knees	68 (85.0%)
Medication	
Non-steroidal anti-inflammatory	79 (98.75%)
Glucosamine	12 (15.00%)
Prednisone	9 (11.25%)
Relaxon	2 (2.50%)
Methotrexate	6 (7.50%)
Number of fat injection	
Single injection	76 (95.00%)
Two injections	1 (1.25%)
Three injections	3 (3.75%)

Data are expressed as mean ± SD (minimum-maximum) or number (%) as appropriate.

4. Discussion:

Chronic degenerative osteoarthritis of knee joints is a common progressive, degenerative, debilitating joint disease. It is typified by inflammation, loss of intra-articular cartilage, formation of osteophytes, thickening of the capsule which causes pain, stiffness and limitation of physical activity and negatively affects the quality of life.[18,19]

Spontaneous healing of degenerated or damaged articular cartilage, especially partial thickness defect, is rare due to poor vascularization and absence of direct access of the cartilaginous defect to progenitor cells of bone marrow.[16] Our previous innovative study reported that intra-articular injection of autologous fat micro-graft in both the animal and human trial yielded encouraging results and may offer a great hope for the treatment of joint osteoarthritis. Histological evidence in our animal model[12,13] and in other studies showed that these mesenchymal stem cells had the ability to differentiate into various types of cells such as chondrocytes, osteocytes and other skeletal and nerve cells.[20-22]

Recent studies have also demonstrated that mesenchymal stem cells can be isolated from most adult body tissues, including fat.[23-25] The capability of the MSCs in repair and regeneration of mesenchymal tissues, including cartilage defect regeneration, and its efficacy as a therapeutic modality for a wide variety of diseaseshad been widely studied. However, there are still unknown mechanisms of tissue repair using mesenchymal stem cells. It is not yet known whether the transplanted mesenchymal stem cells directly fill the lesion and regenerate the defect articular cartilage

or if they indirectly stimulate the secretion of bioactive factors such as cytokines and growth factors.[26-35]We believe that both mechanisms might be involved in the regeneration. The histological finding in the animal experiment of intra-articular injection of autologous fat micro-graft into hind knee joint showed evident regenerative effects in the form of thickening of the articular hyaline cartilage with chondrocyte proliferation in different mitotic stages.[12]

Table 3. Visual analogue scale values at rest & with activity before and after intra-articular fat micro-graft injection.

Visual Analogue Scale	Pre-Injection	Post-Injection	Significance (*P*-value)
Rest	7.37 ± 1.85(2.00-10.00)	0.69 ± 0.64(0.00-2.00)	**0.0001**
Exercise	9.11 ± 1.52 (6.00-10.00)	1.31 ± 0.79 (0.00-3.00)	**0.0001**

Wilcoxon test for non-parametric variables was used to compare pre- to post-injection values.

Table 4. The Western Ontario and McMaster Universities Osteoarthritis Index before and after intra-articular fat micro-graft injection.

Western Ontario and McMaster Universities Osteoarthritis Index	Pre-Injection	Post-Injection	Significance (*P*-value)
Pain			
1. Walking	3.89 ± 0.32 (3.00-4.00)	0.63 ± 0.54 (0.00-2.00)	**0.0001**
2. Stair Climbing	3.95 ± 0.27 (2.00-4.00)	1.01 ± 0.46 (0.00-2.00)	**0.0001**
3. Nocturnal	3.30 ± 0.75 (0.00-4.00)	0.33 ± 0.61 (0.00-4.00)	**0.0001**
4. Rest	3.13 ± 0.77 (0.00-4.00)	0.15 ± 0.36 (0.00-1.00)	**0.0001**
5. Weight bearing	3.98 ± 0.22 (3.00-4.00)	0.96 ± 0.49 (0.00-2.00)	**0.0001**
Stiffness			
1. Morning stiffness	3.29 ± 0.96 (0.00-4.00)	0.30 ± 0.46 (0.00-1.00)	**0.0001**
2. Stiffness occurring later in the day	2.95 ± 1.04 (0.00-4.00)	0.39 ± 0.49 (0.00-1.00)	**0.0001**
Physical Function			
1. Descending stairs	3.86 ± 0.45 (3.00-4.00)	0.86 ± 0.38 (0.00-2.00)	**0.0001**
2. Ascending stairs	3.96 ± 0.19 (3.00-4.00)	0.89 ± 0.45 (0.00-2.00)	**0.0001**
3. Rising from sitting	3.60 ± 0.63 (2.00-4.00)	0.21 ± 0.41 (0.00-1.00)	**0.0001**
4. Standing	3.50 ± 0.67 (2.00-5.00)	0.48 ± 0.55 (0.00-2.00)	**0.0001**
5. Bending to floor	3.14 ± 0.85 (0.00-4.00)	0.35 ± 0.53 (0.00-2.00)	**0.0001**
6. Walking on flat surface	3.15 ± 0.71 (2.00-4.00)	0.18 ± 0.38 (0.00-1.00)	**0.0001**
7. Getting in / out of car	3.49 ± 0.56 (1.00-4.00)	0.71 ± 0.56 (0.00-2.00)	**0.0001**
8. Going shopping	3.89 ± 0.39 (2.00-4.00)	1.04 ± 0.51 (0.00-2.00)	**0.0001**
9. Putting on socks	2.95 ± 0.84 (0.00-4.00)	0.36 ± 0.58 (0.00-3.00)	**0.0001**
10. Lying in bed	2.95 ± 0.90 (0.00-4.00)	0.16 ± 0.37 (0.00-1.00)	**0.0001**
11. Taking off socks	2.60 ± 0.76 (0.00-4.00)	0.18 ± 0.41 (0.00-2.00)	**0.0001**
12. Rising from bed	3.18 ± 0.79 (1.00-4.00)	0.20 ± 0.40 (0.00-1.00)	**0.0001**
13. Getting in/out of bath	3.71 ± 0.66 (1.00-4.00)	0.86 ± 0.66 (0.00-2.00)	**0.0001**
14. Sitting	3.05 ± 0.88 (0.00-4.00)	0.26 ± 0.55 (0.00-3.00)	**0.0001**
15. Getting on/off toilet	2.94 ± 0.77 (2.00-4.00)	0.36 ± 0.45 (2.00-4.00)	**0.0001**
16. Heavy domestic duties	3.95 ± 0.27 (2.00-4.00)	1.10 ± 0.56 (0.00-4.00)	**0.0001**
17. Light domestic duties	2.50 ± 0.76 (0.00-4.00)	0.14 ± 0.38 (0.00-2.00)	**0.0001**
Total score			
Out of 96	81.09 ± 9.87 (41.00-96.00)	12.10 ± 6.26 (0.00-33.00)	**0.0001**
Percentage (%)	84.47 ± 10.28 (42.71-100.00)	12.60 ± 6.52 (0.00-34.38)	**0.0001**

The activities in each category are rated according to the following scale of difficulty: 0 = No difficulty; 1 = Slight difficulty; 2 = Moderate difficulty; 3 = Very difficult; 4 = Extremely difficult. Data are expressed as mean ±- SD (minimum- maximum). Wilcoxon test for non-parametric variables was used to compare pre- to post-injection values.

Our current extended clinical study clearly confirmed the findings of the previous preliminary study that the intra-articular injection of native non-processed autologous fat micro-graft has a lubricating and healing effect on the osteoarthritic joints; as clinical evaluation showed an improvement of pain pre- versus post-fat injection on visual analogue scale during rest and with activity (Table 3).

. The three domains of pain, stiffness and physical function on the WOMAC index were also significantly lower in the post intra-articular fat injection period compared to the pre-injection values. The WOMAC test total score and its percentage were significantly lower in the post intra-articular fat injection period compared to the pre-injection values (Table 4).

Clinical studies on the application of mesenchymal stem cells for cartilage regeneration are still limited. Although several studies, including ours, have reported promising results on the potential of mesenchymal stem cells in regenerative joint therapy, more preclinical and clinical studies are necessary to establish the appropriate conditions and techniques for the application of mesenchymal stem cells in humans. It is our project to progress with further modifications to improve the outcome and further clarify the mechanism of action.

Conclusion:

This extended study with 80 patients (148 joints) confirmed the results of our innovative and first reported previous preclinical animal and preliminary human studies that the intra-articular injection of autologous fat micro-graft in the treatment of knee osteoarthritis offers the hope of an effective and safe treatment method. It has a lubricating influence with regenerative and reparative effects which help to restore the lost cartilage, improve joint mobility, increase the range of movement and raise the quality of life. Further longitudinal study of these patients is needed to find out any side effects and durability of fat as stem cells for treatment of osteoarthritis.

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