Fresh autologous stromal tissue fraction for the treatment of knee osteoarthritis related pain and disability

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Abstract

Knee osteoarthritis (KOA) is a very common condition with multifactorial etiology leading to severe pain and disability in the adult population. Although KOA is considered a non-inflammatory arthritis, upregulation of inflammatory and catabolic pathways with increased production of pro-inflammatory cytokines leading to cartilage degradation and extracellular matrix degeneration has been reported. Intra-articular injection of fresh fat derived stromal vascular fraction (SVF) fraction has been proposed as a valid and alternative treatment for symptomatic KOA that guarantees mechanical support through viscosupplementation, anti-inflammatory, and anabolic action. We retrospectively reviewed a case series of 84 consecutive adult patients with KOA who underwent intra-articular injection of fresh fat derived SVF. Significant improvement in pain levels (NRS score decrease 3.5±1.1, p<0.001), WOMAC pain (-7.02±3.45 score change, p<0.001), WOMAC stiffness (-1.97±1.02, p<0.001), and ROM improvement (+17.13±5.22°, p<0.001). The only complication noted was knee joint swelling lasting for less than 7 days after the injection in 7% of the patients.

Introduction

Knee osteoarthritis (KOA) is one of the leading causes of disability worldwide. According to the World Health Organization (WHO) more than 10% of people over 60 years suffers from KOA, with an higher incidence in women.[1] Several risk factors for KOA have been identified including mechanical (trauma, fractures, and cartilage wear and tear), constitutional (age, sex, and increased body mass index), and genetic.[2] Nevertheless, age remains the main risk factor for KOA, as it becomes more common in patients older than 70 years-old.[3] On the other hand, main causes of KOA in younger patients are sport injuries, occupational activities, and obesity.[4] In athletes, repetitive impacts and loading of the joint can cause articular cartilage damage and higher rates of KOA.[5] Regardless of its causes, symptoms of KOA are stiffness, reduced range of motion (ROM), crepitus, and joint swelling with pain.

Although KOA is considered as a non-inflammatory arthritis, upregulation of pro-inflammatory pathways has been reported.[3] Chondrocytes, osteoblasts and inflamed synovium all produce pro-inflammatory cytokines involved in the catabolic process in KOA.[2] This is in line with the reported efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) and steroids in treatment of KOA. Intra-articular hyaluronic acid injections have also been used with good results on KOA thanks to its anti-inflammatory, local analgesic, anabolic, and chondroprotective activities with a very low rate of adverse reactions.[6] However, long term efficacy of these therapies has been questioned by several authors.[7]

Zuk *et al*.[8] first reported on the possibility of obtaining high quantity of mesenchymal stem cells (MSC) from harvested adipose tissue with low morbidity related to the harvesting technique. More recently, intra-articular injection of adipose-derived stem cells and stromal vascular fraction (SVF) has been shown to be effective in reducing inflammation and pain and increasing range of motion (ROM) in osteoarthritis affected joints.[9]

The aim of this study was to evaluate the benefits of intra-articular injection of fresh fat derived stromal vascular fraction (SVF) in terms of pain and function improvement in a consecutive series of adult patient affected by knee OA.

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Materials and Methods

Following Institutional Review Board (IRB) approval as part of service evaluation, we retrospectively reviewed all consecutive patients who underwent knee intra-articular injection with fresh fat derived stromal vascular fraction (SVF) for symptomatic KOA from January 2014 to December 2017. All patients gave their written informed consent at enrolment for the procedure and were included into a prospective observational database. The inclusion criteria were: age ≥18 years; symptomatic KOA (NRS score ≥4) not responsive to at least 6 months course of physical therapy and oral pain killers; radiographic confirmed KOA (as defined as Kellgren-Lawrence score ≥2); no previous knee surgery. All patients had no concomitant infection, history of cancer or allergy.

All patients underwent knee intra-articular injection with fresh SVF derived from autologous body fat. The adipose tissue, obtained by handmade soft liposuction, was intraoperatively separated with a specific kit (MyStem™ kit, MyStem, Italy). SVF

extraction was performed in the operating room under sterile conditions according to manufacturer instructions. Briefly, local tumescent anesthesia was performed using a solution of 100 ml of normal saline, adrenaline 0.1 mg and lidocaine 2% 8 mL; abdominal subcutaneous tissue was harvested with manual minimally invasive liposuction (Figure 1). The harvested tissue is then transferred to the collection bag where the adipose portion is separated from the fluid portion (Figure 2). The fluid portion is then filtered again through the MyStem™ kit (Figure 3) to obtain a purified fluid containing the concentrated SVF portion (Figure 4). The adipose portion is collected (Figure 5), fragmented (Figure 6), and finally mixed with the purified SVF portion to work as a scaffold ensuring shock adsorption and viscosupplementation once injected into the articular space (Figure 7).

Pain and knee function were evaluated in all the patients at base-line (before injection) and at 12 months after intra-articular injection therapy by NRS pain score and WOMAC scale.

Results

A total of 84 patients (46 females) with radiographic confirmed knee osteoarthritis (Kellgren-Lawrence score ≥2) were included in the current study. The average age was 57.3±4.2 years (range 34-79). Twenty-two patients, representing 26% of the sample, were ≤45 years-old at enrolment and were affected by post-traumatic KOA. The remaining 62 patients (74% of the sample) were ≥45 years-old and were affected by degenerative and/or post-traumatic KOA. In 18 patients (10 females and 8 males) bilateral injection was performed.

Only patients with pre-operative NRS score ≥4 were enrolled. Average pre-operative NRS score was 5.8±1.3 and improved to 2.3±0.9, 12 months after intra-articular therapy with SVF ($p<0.001$). WOMAC pain score improved from 9.67±3.45 to 2.65±3.45 ($p<0.001$), while WOMAC stiffness score improved from 3.15±1.33 to 1.18±1.02 ($p<0.001$). Significant improvement in knee ROM was noted as well (Table 1).

All patients reported a consistent improvement in terms of pain and disability, with the exception of four patients (4.8%). Sixty percent of patients were able stop all pain medication after the procedure, while the remaining 40% were able to reduce their daily intake of analgesics.

No major complications were observed during the study period. Fifteen percent of patients experienced discomfort and pain at the site of adipose tissue harvest for more than three days postoperatively but none of them reported any residual pain more than 20 days after the procedure. Knee swelling and pain was noted in 7% of patients for the first 7 days following the procedure, which was successfully treated with acetaminophen and cryotherapy.

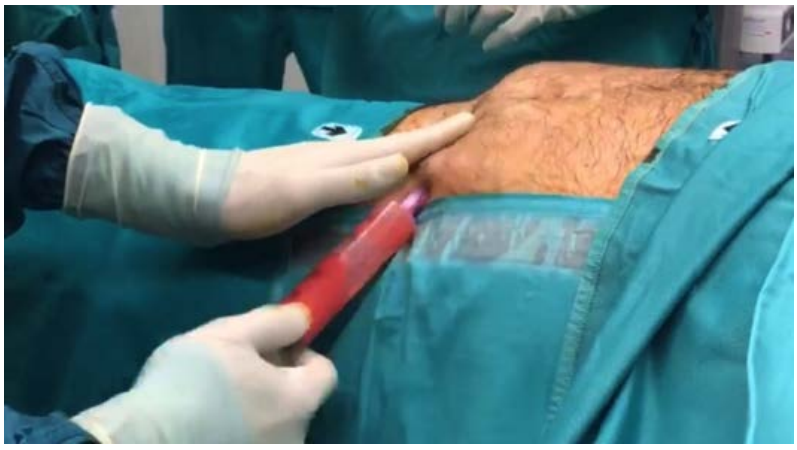

Figure 1. Harvesting fat tissue.

Figure 2. Mechanical separation of fluid portion from adipose portion.

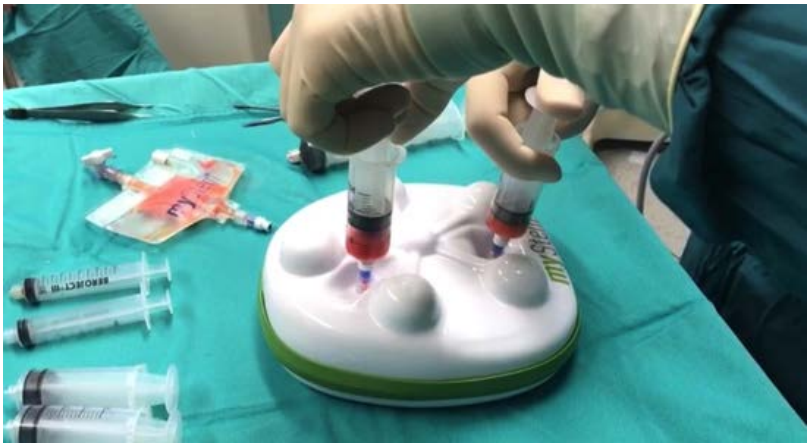

Figure 3. Filtration through MyStem® kit.

Table 1. Pre- and post-injection clinical scores.

	Baseline	1-year	p
NRS	5.8 ± 1.3	2.3 ± 0.9	<0.001
ROM (°)	118.22 ± 14.72	17.13 ± 5.22	<0.001
WOMAC pain	9.67 ± 3.45	-7.02 ± 3.45	<0.001
WOMAC stiffness	3.15 ± 1.33	-1.97 ± 1.02	<0.001

Data are expressed as average ± standard deviation; NRS, numeric rating scale; ROM, range of motion; WOMAC, Western Ontario and McMaster University.

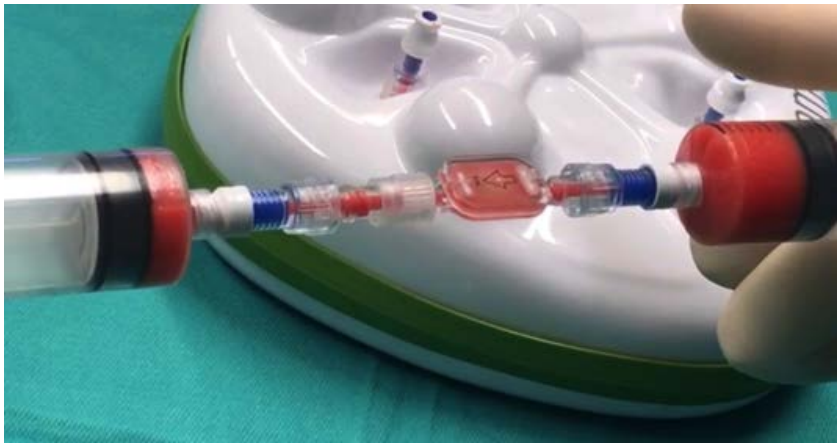

Figure 4. Concentration of mesenchymal cells.

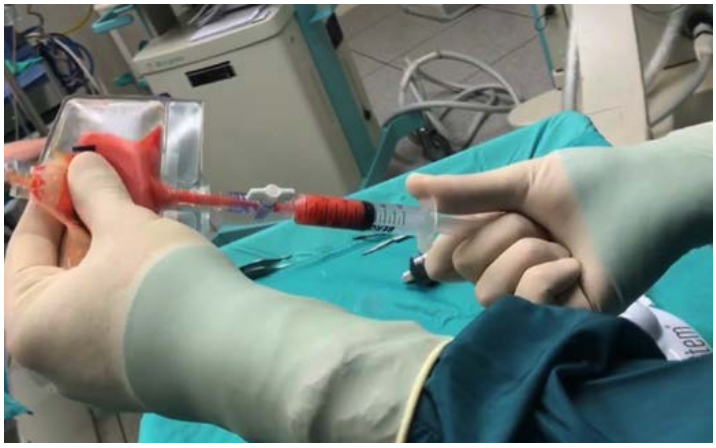

Figure 5. Retake of the adipose portion.

Figure 6. Mechanical fragmentation.

Discussion

KOA is highly prevalent in patients older than 65 years and a significant source of pain and disability. Aging is the main risk factor of KOA as it is associated with progressive structural changes in articular cartilage extracellular matrix (ECM), including decreased type II collagen and proteoglycans content. Advanced glycosylation end products also accumulate within the cartilage, leading to increased cross-linking and altered biomechanical properties. Activation of the inflammatory cascade and progressive imbalance between anabolic and catabolic cytokines is responsible for cartilage degradation. In KOA pro-inflammatory cytokines such as IL-1, TNF-α, and MMP-13 are up-regulated. The inflammatory cytokines act by decreasing extracellular matrix synthesis and increasing matrix degradation through MMP enzymes up-regulation.[10-12] These changes lead to a progressive loss in the ability of cartilage to adapt to mechanical stress and load, as well as pain and joint stiffness.[10]

Over the years, significant research efforts have been made in trying to prevent progressive cartilage degradation by decreasing pro-inflammatory response in KOA. Preclinical and clinical investigation of the possible role of mesenchymal stem cells (MSCs) in the treatment of chondral defects is an area of active research.

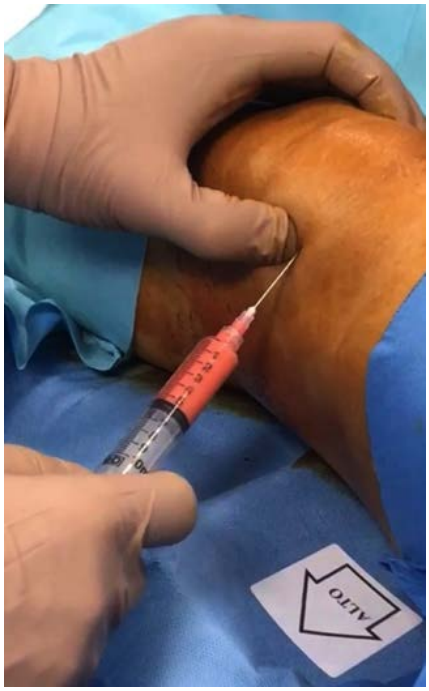

Figure 7. Intra-articular injection.

According to Squillaro *et al*.[13] a total of 493 MSC clinical trial are listed in the US National Institute of Health (NIH) database. In 2001, Zuk *et al*.[8] demonstrated that adipose-derived stromal/stem cells (ADSCs) can be differentiated into chondrocytes, adipocytes, and osteoblasts paving the way for a host of studies into the application of autologous ADSCs in regenerative medicine. Adipose tissue is a promising source of stem cells because of its simplicity in harvesting and very low morbidity. According to Yoshimura *et al*.[14] ADSCs represent up to 10% (2-10%) of stromal vascular fraction (SVF) and their results suggested that human ADSCs might be useful in cell-based therapy approaches.

In vivo and *in vitro* studies have shown that ADSCs have both an anti-inflammatory and anabolic effect on chondrocytes and synoviocytes.[15] ADSCs act by secreting large amounts of bioactive molecules in response to the joint local environment.[16] The immunoregulatory effect of intra-articular stem cells leads to down-regulation of pro-inflammatory cytokines, inhibition of T-cell recognition and expansion by inhibiting TNF-α and IFN-γ production, and increase of IL-10 levels. The bioactive molecules secreted by ADSCs also inhibit scarring, cellular apoptosis, stimulate angiogenesis by releasing VEGF, and stimulate mitosis of intrinsic tissue progenitor and stem cells.[17,18]

Our study shows provides useful clinical data on the efficacy of intra-articular injection of fresh SVF in relieving symptoms of KOA at a relatively long follow-up (*i.e.* 12 months). Safety profile of the procedure also was confirmed in our case series. Similarly, Hong *et al*.[19] compared the efficacy in terms of radiographical and clinical outcomes of SVF and hyaluronic acid injection in knee osteoarthritis and demonstrated that SVF provide superior improvements at 1-year follow-up. Our study has some limitations. Systematic MRI evaluation at baseline and at 12 months follow up was not performed. Minimum follow-up was 12 months, but we are still following our patients to assess longer term outcomes. Finally, our case series includes both post-traumatic KOA as well as age related KOA.

Conclusions

In conclusion, knee joint fresh SVF injection for symptomatic treatment of KOA (Kellgren-Lawrence ≥2) is a safe and effective procedure with a very low rate of morbidity both in the harvesting and injecting process. Significant improvement in terms of pain (NRS scores) and knee function (WOMAC score and ROM improvement) have been observed in our case series of adult patients with KOA.

References

1. Buckwalter JA MJ. Osteoarthritis. Adv Drug Deliv Rev 2006;58:150-67.
2. Hussain SM, Neilly DW, Baliga S, et al. Knee osteoarthritis: A review of management options. Scott Med J 2016;61:7-16.
3. Dieppe PA, Lohmander L. Pathogenesis and management of pain in osteoarthritis. Lancet 2005:18:965-73.
4. Buckwalter JA. The Role of Mechanical Forces in the Initiation and Progression of Osteoarthritis. HSS J 2012;8:37-8.
5. Buckwalter JA, Lane NE. Current Concepts: Athletics and Osteoarthritis. Am J Sports Med 1997;25:873-81.
6. Hepper CT, Halvorson JJ, Duncan ST, et al. The efficacy and duration of intra-articular corticosteroid injection for knee osteoarthritis: A systematic review of level I studies. J Am Acad Orthop Surg 2009;17:638-46.
7. Zuk PA, Zhu MIN, Mizuno H, et al. Multilineage Cells from Human Adipose Tissue: Implications for Cell-Based Therapies. Tissue Eng 2001;7:211-28.
8. Watterson JR, Esdaile JM. Viscosupplementation: therapeutic mechanisms and clinical potential in osteoarthritis of the knee. J Am Acad Orthop Surg 2000;8:277-84.
9. Fodor PB, Paulseth SG. Adipose Derived Stromal Cell (ADSC) Injections for Pain Management of Osteoarthritis in the Human Knee Joint. Aesthetic Surg J 2016;36:229-36.
10. Martin Lotz RFL. Effects of aging on articular cartilage homeostasis Martin. Bone 2012;51:241-8.
11. Sandell L, Aigner T. Articular cartilage and changes in arthritis. An Introduction: Cell biology of osteoarthritis. Arthritis Res 2001;3:107-13.
12. Henrotin Y, Kurz B, Aigner T. Oxygen and reactive oxygen species in cartilage degradation: Friends or foes? Osteoarthr Cartil 2005;13:643-54.
13. Squillaro T, Peluso G, Galderisi U. Clinical Trials With Mesenchymal Stem Cells: An Update. Cell Transplant 2016;25:829-48.
14. Yoshimura K, Shigeura T, Matsumoto D, et al. Characterization of Freshly Isolated and Cultured Cells Derived From the Fatty and Fluid Portions of Liposuction Aspirates. J Cell Physiol 2006;208:64-76.
15. Bansal H, Comella K, Leon J, et al. Intra-articular injection in the knee of adipose derived stromal cells (stromal vascular fraction) and platelet rich plasma for osteoarthritis. Off Board Mark 2001;77:1-11.
16. Caplan AI. Why are MSCs therapeutic? New data: new insight. J Pathol 2008;217:318-24.
17. Caplan AI. Adult Mesenchymal Stem Cells for Tissue Engineering Versus Regenerative Medicine. J Cell Physiol 2007;213:341-7.
18. Caplan AI, Correa D. The MSC: An Injury Drugstore The Mesenchymal Stem Cell (MSC). J Stem 2011;9:11-5.
19. Hong Z, Chen J, Zhang S, et al. Intra-articular injection of autologous adipose-derived stromal vascular fractions for knee osteoarthritis: a double-blind randomized self-controlled trial. Int Orthop. 2018.