Journal of Clinical Orthopaedics and Trauma xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Clinical Orthopaedics and Trauma

journal homepage: www.elsevier.com/locate/jcot

Microfragmented adipose injections in the treatment of knee osteoarthritis

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ARTICLE INFO

Article history:
Received 7 September 2018
Received in revised form
25 October 2018
Accepted 30 October 2018
Available online xxx

1. Introduction into the role of adipose tissue for orthopedic conditions

As the projected growth of the aging population continues to rise, more and more adults are affected by degenerative orthopedic conditions. Osteoarthritis is the most common degenerative joint disease and can lead to pain and functional deficits that affect quality of life. Initial management includes weight loss, exercise, oral analgesic and anti-inflammatory medications, physical therapy, corticosteroid and hyaluronic acid injections. Many patients continue to remain symptomatic even after conservative treatments are exhausted. Total knee arthroplasty (TKA) is the current accepted treatment of choice for symptomatic knee OA that has not responded to traditional conservative therapies. There are approximately 700,000 TKAs performed annually within the United States. Of particular concern is the rising incidence of TKAs in individuals between 40 and 50 years of age.[1] Additionally, it is estimated that the number of annual total knee revision operations performed annually will grow by over 600% between 2005 and 2030.[1] In addition, these surgeries are not without complications and as many as 19% of patients continue to have knee pain and other problems following TKA.[2] Significant complications such as infections, pulmonary embolism, and death are rare but remain a concern for patients.[3]

Regenerative medicine treatments such as platelet rich plasma, bone marrow aspirate, and adipose derived mesenchymal stem cells, have become attractive alternatives for patients who fall within the "osteoarthritis treatment gap," defined by London et al. as the time period from not responding to conservative treatment options to undergoing surgery.[4] Mesenchymal stem cells (MSCs) are multipotent adult stem cells that self-renew and have the ability to differentiate into various cell types, such as muscle, bone, and cartilage.[5] These cells can be obtained from a patient and subsequently injected into a site of interest in the same patient (ie, autologous use). MSCs also demonstrate paracrine activity by releasing various growth factors and exhibit immunomodulatory capability.[5]

Although studied for several decades, most of the research has focused on bone marrow aspirate concentrate (BMAC). However, in the last 5 years there has been increasing interest in the potential of adipose tissue to combat orthopedic conditions. Adipose derived stromal cells (ADSCs) are MSCs that are isolated from homogenized adipose tissue located in the capillary and perivascular adventitia of large blood vessels within adipose tissue. Compared to BMAC, studies have noted that ADSCs are present in higher numbers per unit volume of tissue, more rapidly proliferate in culture, and are less susceptible to senescence secondary to culture expansion.[5]

A number of studies have demonstrated the benefits of adipose derived mesenchymal stem cells on improving knee joint pain and function. Using a rat OA model, Li et al. demonstrated that fluorescent labeled ADSCs injected into an arthritic knee were detected in soft tissue structures 10 weeks post injection. There was evidence of increased cartilage thickness and improved tissue preservation via the modified O'Driscoll histological score. This study is one of the first to mark the physical presence of MSC in joints with duration of efficacy.[6] A retrospective study by Koh et al.

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https://doi.org/10.1016/j.jcot.2018.10.021
0976-5662/

demonstrated improvement in cartilage whole organ MRI score (WORMs) as well as improved pain scores using the Western Ontario and McMaster University Arthritis Index (WOMAC), Lysholm score, and visual analogue scale (VAS) after intra-articular injection of ADSC, suggesting that both clinical and radiological benefits are related to its use.[7] In addition, Koh et al. also found in a cohort of elderly patients improvement or maintained cartilage status in 87.5% (14/16) of patients after intra-articular knee injections of ADSCs at the time of second look arthroscopy. They concluded that adipose-derived stem cell therapy for elderly patients with knee OA was effective in cartilage healing, reducing pain, and improving function.[8] Concerns regarding the safety profile of adipose derived therapies in humans were highlighted in a study by Jo et al., with primary outcomes being safety and reduction in pain. This study concluded that this treatment was safe, and after administration of high dose ADSC ($1 \times 10^{\wedge}8$), WOMAC scores decreased at 6 months whereas cartilage quality improved without adverse events.[9]

In 2014 Bui et al. reported a case series involving 21 patients with osteoarthritis of the knees. The patients were treated with autologous adipose stromal vascular fraction (SVF) with platelet rich plasma (PRP). The adipose SVF was obtained from digesting 50–100 ml of lipoaspirates originating from the abdomen. Subsequently, the autologous adipose SVF with autologous PRP was injected percutaneously into the diseased knees. After 8.5 months, all patients showed improved VAS pain score and the Lysholm score. There was also a significant increase in the thickness of the cartilage, as depicted on MRIs.[10]

Fodor et al. reported clinical improvement of 8 patients with knee OA treated with autologous adipose stromal vascular cells obtained by enzymatic processing of lipoaspirate. All patients attained full activity with decreased knee pain. WOMAC scores, VAS pain scale score, range of motion (ROM), and timed up-and-go (TUG) results all improved. The improvement in WOMAC scores and VAS scores were maintained at 1 year.[11]

2. FDA concerns and guidance on the use of adipose tissue for regenerative procedures

A growing body of research, both in vitro and in vivo, has shown multipotent adipose derived stem cells are an abundant source of mesenchymal stem cells. In the past, these cells were isolated using enzymatic processing of stromal vascular fraction suspensions. These methods proved challenging, not only due to cumbersome harvesting techniques but also due to regulatory concerns regarding cell expansion and manipulation. On November 16, 2017, the FDA updated its regulatory guidelines for the appropriate use of all stem cell therapies, including those derived from adipose tissue.[12] The use of ADSCs must be autologous, which entails that all individuals undergoing treatment serve as both the donor and the recipient, with strict regulations that include same day, non-expanded use of harvested cells. Additionally, the use of adipose tissue must meet “minimal manipulation,” which is defined as “processing of the human cells, tissues, and cellular tissue-based product (HCT/P) that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.” Since adipose tissue is classified as structural tissue, its processing should not alter the original relevant characteristics relating to its utility to provide cushioning and support.

The FDA expresses reservations that the manufacturer processes adipose tissue by removing the cells (such as after enzymatic digestion), leaving the decellularized extracellular matrix portion. This would generally be considered more than minimally manipulated because this processing alters the original relevant characteristics of the adipose tissue relating to its utility to provide cushioning and support. Likewise, the FDA states that the HCT/P must be meant for “homologous use,” meaning that “the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P must perform the same basic function or functions in the recipient as in the donor.”

Currently, there are FDA cleared devices for the harvesting, concentrating, and transferring of autologous adipose tissue for musculoskeletal applications. These devices incorporate “sizing and washing” technology that have been defined by the FDA to preserve the cell and tissue microarchitecture of the adipose tissue, eliminate residues of oil emulsion and blood, and provide a tissue that is minimally manipulated in accordance with the FDA guidelines.

3. Basic science of microfragmented adipose tissue (MFAT)

A new device has been developed and used in a variety of settings to harvest autologous ADSCs with minimal manipulation. The Lipogems device harvests and processes a patient's adipose tissue to form a minimally manipulated (without enzymatic digestion or addition of other biological or pharmacological agents) product. Using a small incision, fat tissue is aspirated from the donor site and gently microfragmented and washed to remove oil and blood residues. The final product is a uniform composite containing many pericytes and MSCs that enhance the natural regenerative properties of the recipient tissue. Mesenchymal stem cells initiate not only direct, but also paracrine effects.[13] Throughout the procedure, the processed fat is subjected to only slight mechanical forces, with no detrimental effects on the integrity of the stromal vascular niche and or the tissue itself.[14] Thus, the main structural and morphologic unit, the adipose niche, is maintained after processing and protects the activated MSCs, strengthening their effectiveness in the recipient environment. The gentle mechanical method produces a ready-to use product in less than 20 min. The procedure is fast, safe, and does not require stem cell expansion or manipulation, and therefore, it is not subjected to the regulatory restrictions imposed by current Good Manufacturing Practice (cGMP) Guidelines.[15]

4. Current literature to support the role of microfragmented adipose tissue (MFAT) for orthopedic conditions

The literature to support the role of MFAT in osteoarthritis remains is sparse but a number of studies have demonstrated promising results. In 2014 Striano et al. demonstrated in a single case report, improvements in VAS pain score and Knee Injury and Osteoarthritis Score (KOOS) outcome 6 months after injecting autologous micro-fragmented adipose tissue in a severely arthritic knee with concurrent meniscal disease. The results are encouraging and pave the way for larger studies for patients with knee pain that are not responsive to other current treatments.[16]

Recent literature has demonstrated the safety of MFAT. Russo et al. evaluated the 1-year safety and outcome of a single intra-articular injection of autologous and micro-fragmented adipose tissue in 30 patients affected by diffuse degenerative chondral lesions. They found no major complications, neither at the knee nor at the harvest site level.[17]

Hudetz et al. showed positive structural and biochemical changes in cartilage after intra-articular injection of autologous MFAT in patients with knee OA. A total of 17 patients were enrolled in the study, and 32 knees with OA were assessed. They found a decrease in average visual analogue scale (VAS) scores and an increase glycosaminoglycan (GAG) content in hyaline cartilage.[18]

Cattaneo et al. retrospectively analyzed the safety and potential benefits of using autologous and micro-fragmented adipose tissue

Please cite this article as: Malanga GA, Bemanian S, Microfragmented adipose injections in the treatment of knee osteoarthritis, Journal of Clinical Orthopaedics and Trauma, https://doi.org/10.1016/j.jcot.2018.10.021

as adjuvant in the surgical treatment of degenerative knee chondropathy. The results demonstrated that, when associated with a shaving procedure, it improves symptoms and function at least until 1-year follow-up, with a trend of steady increase during time. Indeed, a constant and statistically significant improvement of all the clinical scores was observed from pre-op evaluation to the 1, 3, 6, and 12 months follow-up with KOOS sport and quality of life being the most improved scores.[19]

A recent study by Malanga et al. demonstrated the safety and efficacy of percutaneous injection of MFAT in 17 patients with a history of knee OA (Kellgren Lawrence grade 3 and 4). Significant improvements were noted in pain and functional outcome measures at 12 months compared to baseline. They noted improvement of the Numerical Pain Rating Scale (NPRS), Knee Society Score (KSS), and Lower Extremity Activity Scale (LEAS). No serious adverse effects were reported.[20]

5. Current research on microfragmented adipose tissue (MFAT) for orthopedic conditions

A search of clinicaltrials.gov reveals a number of ongoing studies assessing the effects of microfragmented adipose tissue for knee OA. The first study by Richter from the Univeristy of New Mexico will evaluate the effectiveness of MFAT to reduce joint pain and increase function in patients with knee osteoarthritis in a randomized, placebo controlled trial with 100 participants. Patients will be randomized to receive either MFAT, intra-articular corticosteroids, or a placebo injection of saline. The primary outcome is change in VAS scale overtime and the secondary outcome is a change in the WOMAC and KOOS score overtime.[21]

The use of Hyaluronic acid (HA) is a component of the standard of care for knee osteoarthritis. Another study from the University of Southern California will compare the efficacy of MFAT versus a single injection of hyaluronic acid for the treatment of mild to moderate knee osteoarthritis. This is a randomized, controlled trial with 54 participants.[22]

Lastly, in a single-blind, randomized controlled study, investigators from the Rizzoli Orthopedic Institute in Bolonga, Italy seek to compare the effectiveness and safety of intra-articular injections of MFAT with those of a control group (PRP injection) for the treatment of symptomatic osteoarthritis of the knee. The endpoints will evaluate the performance of the treatment group in terms of symptomatology, functional recovery and radiological appearance.[23]

6. Conclusions

The field of regenerative medicine provides a new area of nonoperative treatment to address various orthopedic conditions including knee osteoarthritis. The potential for improvement of a patient's quality of life by reducing pain and improving function, with minimal adverse effects, has resulted in interest among researchers, practitioners, and the biotech industry to develop novel applications of cellular based therapies. Adipose tissue has demonstrated to be safe and potentially effective in the treatment of orthopedic conditions. Microfragmented adipose tissue is a FDA compliant, a minimally invasive procedure for harvesting and injection adipose tissue for orthopedic conditions. Future randomized controlled studies with larger numbers of participants should be conducted to better determine the efficacy of MFAT for orthopedic conditions including knee osteoarthritis.

Acknowledgements

Dr. Malanga receives honorarium from Lipogems for education and speaking.

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