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EDITORIAL

Adipose-derived stem cells and knee osteoarthritis: New perspectives, old concerns

Eduardo B de Sousa, José Paulo A Gabbi Filho, Vinicius S Gameiro, Leandra S Baptista

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Abstract

In this editorial, we comment on the paper by Muthu *et al* published in the recent issue of the journal. This editorial review focusses on the use of adipose-derived stem cells (ADSCs) in knee osteoarthritis treatment. We discuss the differences between the stromal vascular fraction and microfragmented adipose tissue and highlight the results of clinical studies comparing both treatments and the use of hyaluronic acid, platelet-rich plasma, and bone marrow aspirate concentrate. The use of expanded ADSCs is also discussed; moreover, concerns regarding treatment with ADSCs, particularly the heterogeneity of published studies and the need to standardize protocols to explore clinical potential is explored.

Key Words: Adipose tissue; Adipose-derived stem cells; Stromal vascular fraction; Knee; Osteoarthritis; Microfragmented adipose tissue

Core Tip: Adipose tissue has been described being superior to bone marrow as a source mesenchymal stem cell due to its lower invasiveness and higher cell content. Hence, products derived from the adipose tissue for the treatment of knee osteoarthritis represent a potential perspective of treatment. However, although most papers describe their potential use, papers present heterogenous protocols heterogeneity in for harvesting and delivery represent a concern.

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INTRODUCTION

Knee osteoarthritis (KOA) is a chronic disease that affects the whole synovial joint, leading to cartilage degeneration, synovial inflammation, and subchondral bone thickening[1,2]. KOA treatment involves conservative (non-operative) measures, including education, analgesics and anti-inflammatory drugs, corticosteroids, and physical therapy and exercise. Surgical measures include arthroscopy, osteotomy, and total joint replacement[3,4]. In the last decades, interest in the use of orthobiologics, biologic materials for orthopedic disease treatment, has increased. These include platelet-rich plasma (PRP), bone marrow concentrate, and mesenchymal stem cells owing to their potential role in relieving KOA symptoms, slowing disease progression, and regenerating articular cartilage[5-7]. In the systematic review by Muthu *et al* [8] in 2023, adipose tissue was described as superior to bone marrow as a mesenchymal stem cell source in terms of safety and KOA improvement. However, the authors recommended future trials to confirm their findings. A thorough literature analysis regarding the use of products derived from adipose tissue for KOA treatment leads to the insight that they have treatment potential; however, the heterogeneity of protocols and published studies reveals concerns similar to those reported with other orthobiologic therapies. Beginning with their nomenclature, papers describing various treatments as adipose-derived stem cells (ADSCs) are common. However, ADSC can be observed in distinct proportions in microfragmented adipose tissue (MFAT) and stromal vascular fraction (SVF). For their suitable isolation and expansion in culture, ADSC must be isolated from SVF[9]. Moreover, these sources of ADSC (Figure 1) may differ in their clinical effect[10,11]. Another concern involves patient stratification aiming to predict outcomes[12], especially in KOA as the disease presents different phenotypes[13]. This review aimed to highlight the differences between various ADSC treatments and to present the most recent studies involving their use in clinical practice.

ADSC

The SVF, a cell fraction of adipose tissue without adipocytes, consists of heterogeneous nonadipocyte cell types such as fibroblasts, vascular cells, macrophages, and plastic adherent cells amenable to culture, called ADSC[14-16]. The SVF contains factors that enhance and stimulate regenerative pathways including angiogenesis, cell proliferation, and differentiation[17] and is predominantly obtained through collagenase digestion, centrifugation, washing, and filtration[15,16]. MFAT is a type of adipose tissue processing wherein the lipoaspirate is fragmented into 0.2-0.8 clusters, maintaining stromal cells intertwined in the extracellular matrix content, including ADSCs and pericytes[18]. MFAT produced by different systems may lead to distinct cellular content, consequently affecting the cytokine profile[16,19]. Besides, MFAT extracted from patients with obesity exhibits greater pro-inflammatory cytokine patterns and effects[20]. ADSC are fibroblastic-like cells isolated from the SVF using enzymatic or mechanical processing of adipose tissue[21]. ADSC popularity rose given their ease of harvest, yielding up to 10% of nucleated cells compared to 0.001%-0.01% found in bone marrow-derived stem cells; high proliferative potential and expansion; and low rate of complications[22]. ADSC can be differentiated *in vitro* into adipocytes, osteoblasts, chondroblasts, and myocytes[23]. Moreover, ADSCs do not lose their chondrogenic potential and expansion properties with age, and have greater anti-inflammatory properties[24].

NON-EXPANDED ADSC: STUDIES ON SVF AND MFAT

Jeyaraman *et al*[25] affirmed that level I evidence studies involving the use of SVF for KOA treatment were available and suggested establishing standardized protocols following regulatory requirements. SVF isolation can be alternatively performed using mechanical or physical forces to modify adipose tissue structural integrity and to avoid the potential side effects of enzymatic digestion, preserving cells in their native environment[17,26]. Boada-Pladellorens *et al*[27] suggested that SVF was a safe and promising treatment for KOA, indicating that the products need standardization and cell number homogenization. This finding was confirmed by Goncharov *et al*[28], noting the safety and efficacy of SVF in improving pain, symptoms, and mobility in patients with KOA and presenting with few or no adverse effects. Goncharov *et al*[28] also indicated the need to evaluate the study design, sample size, and method variability, prioritizing patient safety. Aletto *et al*[29] reported excellent clinical and radiographical results using intra-articular SVF for KOA treatment.

Kim *et al*[30] reported that arthroscopically implanted SVF used in the treatment of Outerbridge grade 3-4 cartilage lesions in KOA can result in pain relief and cartilage regeneration, which correlated to magnetic resonance imaging outcomes at 12 months. Santoprete *et al*[31] concluded that SVF is a safe and effective procedure with low morbidity for patients with KOA [Kellgren-Lawrence grade (K-L) ≥ 2]. Hong *et al*[32] indicated that "superior to hyaluronic acid (HA)" SVF treatment was safe, relieved pain, improved function, and repaired cartilage in patients with K-L grades 3-4 KOA. Bolia *et al*[33] suggested that both bone marrow aspirate concentrate (BMAC) and SVF presented short-term symptomatic relief in patients with KOA; however, SVF resulted in better pain reduction. Gobbi *et al*[34] concluded that one MFAT

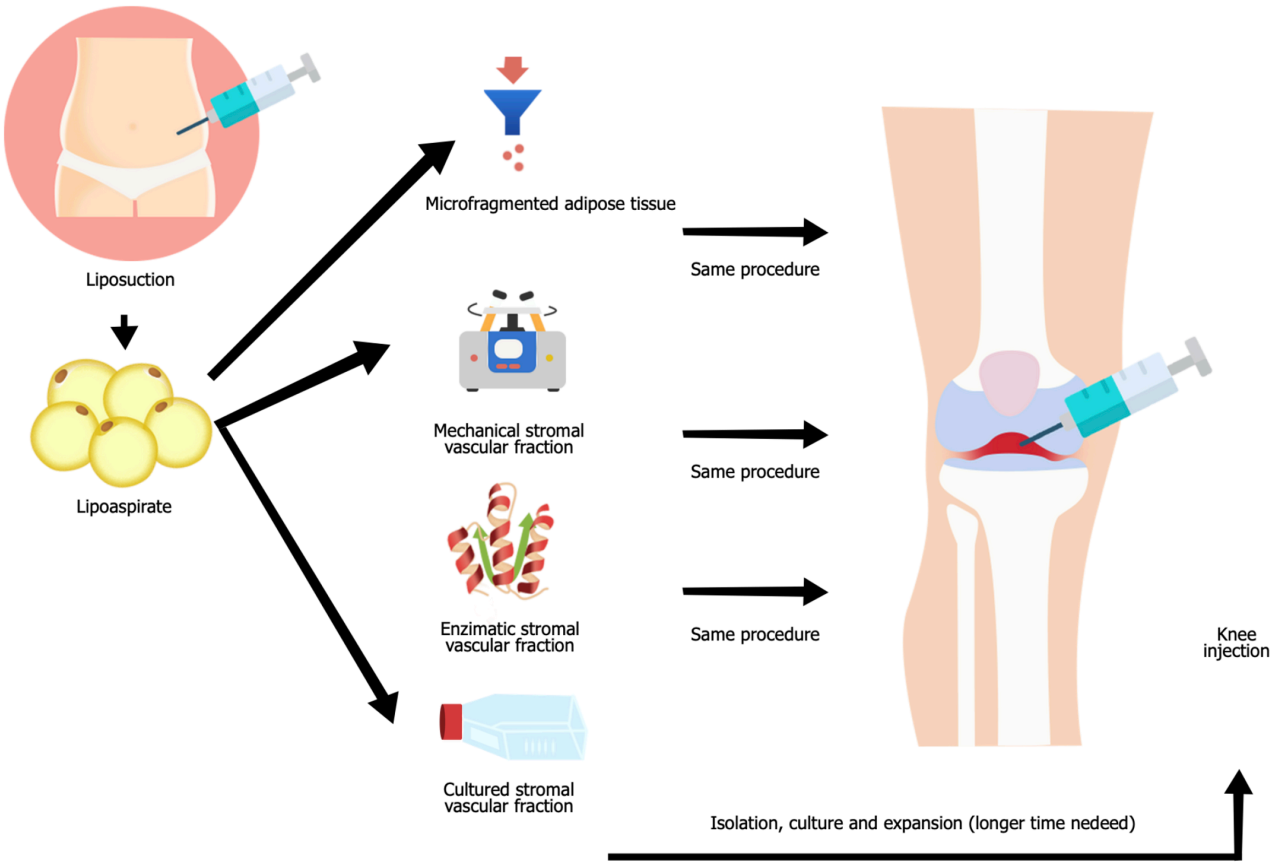

Figure 1 Different sources of adipose derived stem cells according to the processing. Microfragmented adipose tissue is obtained after mechanical fragmentation of the lipoaspirate. Stromal vascular fraction can be obtained by centrifugation, enzymatic digestion, which are processed in the same surgical procedure, or by cell culture, which demands longer time due to culture expansion and is more expansive, besides needing another procedure for infiltration.

injection improved clinical, functional, and quality of life outcomes in K-L grade 2-4 KOA patients at two years. Similarly, Yu *et al*[35] noted that autologous MFAT improved knee pain and function 9-12 months after injections; no adverse effects were observed after 18 months compared to baseline. Wu *et al*[36] observed that compared to HA, treatment with MFAT following arthroscopic surgery was safe and effective given better improvement in pain and function between 12 and 24 months in patients with KOA. Ulivi *et al*[37] concluded that MFAT and arthroscopic debridement improved functional outcomes and magnetic resonance imaging appearance compared to isolated arthroscopy in patients with KOA.

Comparing KOA treatment at six months using PRP and MFAT revealed clinical improvements without differences in outcomes[38,39]. However, a prospective comparative trial concluded that intra-articular injection of BMAC and ADSCs improved pain and function in patients with KOA at six months, without notable differences between them[40]. Oeding *et al*[41] noted that PRP was superior to HA for KOA treatment, confirming the results of Belk *et al*[42], who also suggested that leukocyte-poor PRP would be superior to leukocyte-rich PRP. Belk *et al*[43] also indicated that KOA treatment with PRP or BMAC may improve clinical outcomes when compared to HA. Russo *et al*[44] suggested that MFAT can be used in patients with moderate to severe KOA ineligible for knee replacement owing to the positive relationship between worse preoperative scores and better clinical outcomes. However, Screpis *et al*[45] despite reporting that MFAT was a safe, minimally-invasive treatment for patients with KOA, alerted that worse clinical outcomes would be associated with advanced K-L grade 4 KOA.

STUDIES ON EXPANDED/CULTURED ADSC

Kim *et al*[46] affirmed that expanded/cultured ADSC led to significant pain relief and functional improvement in patients with K-L grade 3 KOA, but suggested that long-term follow-up was required to explore the disease-modifying effects and their duration. Comparing ADSC and leukocyte-poor PRP for KOA treatment, both resulted in good clinical outcomes at six months, but ADSC was superior at twelve and twenty-four months[47]. Huang *et al*[48] concluded that the potential risks and side effects of ADSC must be explored, although it presents promising results in KOA treatment. Furthermore, Issa *et al*[49] observed that ADSC was a safe and effective treatment, presenting short and possibly long-term results on pain and functional outcomes for patients with KOA. Their results corroborate those of Yang *et al*[50] which indicated that single or multiple injections of both ADSC or SVF were safe and improved pain in patients with KOA. Schweich-Adami *et al*[51] reported the treatment of one patient with KOA with expanded ADSC, resulting in an improvement in pain and quality of life. Finally, Yokota *et al*[52] observed that both the intra-articular injection of SVF and ADSC in

patients with KOA led to clinical improvement; however, ADSC revealed superior results in terms of improvement of pain and symptoms, suggesting that a clinical trial should be conducted for further validation.

CONCLUSION

KOA treatment using adipose tissue and associated cells has been increasing currently owing to the ease of harvesting and low morbidity. Moreover, adipose tissue presents higher mesenchymal stem cell content than bone marrow. Based on published studies, ADSC presents better clinical outcomes than HA, PRP, and BMAC. However, most studies describing the potential use of ADSC present heterogeneous protocols for harvesting and delivery. Hence, concerns similar to other orthobiological treatments persist, and more studies are required to establish adequate protocols for their clinical use.

FOOTNOTES

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