Adipose-Derived Mesenchymal Stem Cells as the Panacea for Degenerative Joint Diseases: Fact or Fiction?

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ABSTRACT

The biological approaches have recently gained more attention among orthopedics clinicians and surgeons, and in particular adipose-derived mesenchymal stem cells (AMSCs), due to the invasiveness of the procedure and the good outcomes reported in preliminary trials. In Literature, more than 5,000 articles dealing with the potentialities of ADSC are currently available, but, in our acknowledgement, only few papers focused on clinical results, with contradictory results. In addition, concerns about safety remain among clinicians, because the follow-up time in these analyses was yet limited and a chance of considerable risk is still possible. Nonetheless, long-term adverse events are still poorly researched. As a result, it is impossible to draw a conclusive sentence due to the short follow-up time or small sample size. More high-quality studies should be performed to validate safety of this fascinating approach, first, and then efficacy.

Keywords: Adipose-Derived Stem Cells; Stromal Vascular Factor; Cartilage; Osteoarthritis; Degenerative Joint Disease

Abbreviations: HA: Hyaluronic Acid; MSCs: Mesenchymal Stem Cells; GF: Growth Factors; AMSCs: Adipose-Derived Mesenchymal Stem Cells; IL: Interleukin; SVF: Stromal Vascular Fraction; MRI: Magnetic Resonance Imaging

Introduction

The continuously evolving society of the third millennium requires more and more athletic skills for citizens of all countries. Given the increasing life expectancy, together with the global trend to obesity and the increasing number of sport-related injuries at all ages, degenerative joint pathologies are becoming an enormous medical and socio-economic burden [1]. Non-surgical treatments, such as physio kinesitherapy, pharmacological treatments, hyaluronic acid (HA) or its derivatives, temporarily target the symptoms but cannot prevent the degenerative process [2]. Joint-preserving surgical treatments, such as arthroscopic shaving, provide temporary relief of symptoms [3]. In this context, the biological approaches have recently gained more attention among orthopedics clinicians and surgeons, and in particular mesenchymal stem cells (MSCs), for their ability to act not only on cartilage, but on the whole joint environment [4]. Initially, MSCs were described by Caplan [5] as pluripotent cells, easily isolated from different tissues (including bone marrow, adipose tissue, synovial capsule), which can differentiate into different cell lineages (such as bone, cartilage, muscle, and tendons), contributing in this way to repair the damaged area.

More recently, several clinicians emphasized their paracrine effect to secret various cytokines and growth factors (GF) to adjacent cells, leading to vascularization and cellular proliferation in damaged tissues, and their immunomodulatory properties, so they can reduce inflammation in injured tissues [4]. The definition of Medicinal Signaling Cells, proposed by the same Caplan, represents a more comprehensive attempt to describe the potential of this issue, however not yet fully clarified [6]. Adipose-derived
mesenchymal stem cells (AMSCs), firstly identified in the early 2000s [7], offer some intrinsic advantages that deserves particular attention; AMSCs are easily harvested from subcutaneous tissue in large quantities, with low morbidity of the patients, and can easily be isolated and expanded in vitro [8-11]. Moreover, AMSCs have been shown to be immunoprivileged, with low risk of rejection, and more genetically stable in long term culture, with a greater proliferative rate than MSCs isolated from other tissues, in particular bone marrow [12-15].

In addition, AMSCs induce a trophic effect through the secretion of a large number of GF and anti-inflammatory proteins in response to inflammatory molecules, including prostaglandin 2, hepatocyte growth factor, transforming growth factor-β1, vascular endothelial growth factor; tumor necrosis factor-α , stromal cell-derived factor-1, nitrous oxide, IL (interleukin)-4, IL-6, IL-10, and IL-1 receptor antagonist, that support the angiogenesis, tissue remodeling, and antiapoptotic events [16-18]. However, the real potential of these cells remains unknown, since culture expanded AMSC are usually considered to be a pharmaceutical product requiring government regulatory clearance; due to such government regulatory issues, stromal vascular fraction (SVF) has been more commonly used for various orthopedic applications in clinical settings, representing a further confounding variable. The SVF is obtained after an enzymatic or mechanic process [19], and contains a heterogeneous population of cell types, including preadipocytes, pericytes, monocytes, macrophages, red blood cells, and other adventitial stromal cells [20,21], as well as AMSCs, which account for 30% of the total SVF cells [22].

If the therapeutic properties can be attributed to AMSCs or the surrounding perivascular environment is unclear; but some studies have shown improved results with the application of SVF compared to AMSCs, promoting cartilage and subchondral bone regeneration [23] and forming new cartilage matrix [24]. However, further investigations are required to validate these exciting preclinical results for the application in the clinical practice. During the last years, the clinical potential of AMSCs in the treatment of degenerative joint diseases has been reported in several studies, with conflicting findings. Consequently, the aim of the present study is to review the clinical outcomes of AMSCs (including clinical trials where SVF was under investigation) for the treatment of degenerative joint diseases.

Clinical Results

In Literature, more than 5,000 articles dealing with the potentialities of ADSC are currently available, but, in our acknowledgement, only 23 papers [25-47] are clinical trials focusing on clinical and functional outcomes. Furthermore, only few papers present a high level of methodological quality [26,31,40]. In most cases, the clinical application of AMSCs was evaluated in the knee joint, but also in ankle [29,33] and hip [27,37] was tested. AMSCs (or SVF) was harvested from abdominal fat in all but two studies, where the harvest site was the infrapatellar fat pad [35] and the buttock [38]. The clinical effect was evaluated as surgical adjuvant in 5 papers [26,29,33,40,41], and as injective approach in the other 18 papers [25,27,28,30-32,34-39,42-47]. In all studies, a significant improvement in clinical and functional scores from baseline to last follow up (from 6 months to 28.6 months) was reported; the beneficial effect seems to reach the highest point between 6 months and 1 year of follow up [25,27,34,43,46], but a decreasing trend was recorded at longer follow up [30]. Among the 6 comparative studies, the most significant difference when compared to control group, was recorded for pain relief [26,31,35,40], whereas contradictory functional results were recorded, with better functional scores described in 3 papers [29,31,33], no significant intergroup difference in 2 papers [35,40], and even better functional score in the control group in 1 paper [26].

Predictors of poorer results were greater lesion size [39], body mass index [39] and lower preoperative pain [47]. The effect on cartilage was assessed thanks to magnetic resonance imaging (MRI) or second-look arthroscopy in 20 papers, with significant improvement in all but 3 papers, where worse or unchanged findings were reported in most of patients treated [39,40,46]. As a result, it is impossible to draw a conclusive sentence due to the short follow-up time or small sample size. Contradictory results, heterogeneity in outcome measures, heterogeneity in co-interventions (such as surgery, HA or GF injections), processing methods and injection frequency and timing make it difficult to obtain a general and unambiguous statement among clinicians. In addition, concerns about safety remain among clinicians. Two systematic reviews of clinical trials (including case series) evaluating MSCs administered both locally and systemically with follow-up of up to 75 months found no serious adverse events [48,49]. Moreover, currently, evidence of malignant transformation of MSCs is lacking [48]. It should, however, be noted that the follow-up time in these analyses was yet limited and a chance of considerable risk is still possible. Nonetheless, long-term adverse events are still poorly researched.

Conclusion

In conclusion, it is impossible with actual knowledge to identify the real potential of this fascinating possibility of therapy. Numerous studies are currently in progress to clarify questions that still remain unanswered, regarding the long-term durability of these procedures, the possible modifications that have to be done to achieve better results, and the best-performing biological agents for each given kind of patient and/or grade of disease. In the meanwhile, more high-quality studies should be performed to validate their safety, first, and then efficacy.

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