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Matter for Debate

The utility of adipose-derived stem cells and stromal vascular fraction for oncologic soft tissue reconstruction: Is it safe? A matter for debate

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ABSTRACT

Autologous free-fat grafting (AFG) has emerged as an attractive proposition for soft-tissue reconstruction of various contour defects because it obviates more complex reconstructive options and reduces operative times and donor-site morbidity. Nonetheless, a common complication of this procedure is the resorption of the engrafted fat. Cell-assisted lipotransfer (CAL) is now a well-regarded technique where adipose-derived stem cell (ASC)-rich stromal vascular fraction is admixed with lipoaspirate, increasing the volumetric outcome of fat grafts in light of its potent angiogenic and adipogenic properties. Criticisms, however, remain regarding this modality especially for the treatment of post-oncologic defects. Laboratory data has attested to its propensity to perpetuate tumor cells as a result of its paracrine effects on the host microenvironment. This review article aims to present the underlying facts behind ASC therapy and provide meaningful discourse as to its utility in post-oncologic soft tissue reconstruction.

Introduction

Autologous free-fat grafting (AFG) has now emerged as an attractive proposition for soft-tissue reconstruction of various contour defects because it obviates more complex reconstructive options such as locoregional and free flaps, which require specialized microsurgical and perforator dissection skills. Moreover, there are minimal complications and morbidity to the donor site from the harvesting of lipoaspirate in AFG, with generally shorter operative durations. Nonetheless, AFG faces criticism in view of inconsistent volume retention, resorption of the engrafted fat and fat necrosis, which may necessitate repeat surgeries for the correction of these deficits.[1] This may be attributed to cell death and apoptosis of the fat graft constituents as a result of ischemia, inflammation, trauma and oxidative stress within the host

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environment.[2] The advent of adipose-derived stem cell therapy heralds promise in this field of regenerative medicine because of its multifaceted ability to provide paracrine growth factors as stimuli for the engrafted fat, serve as a natural biological scaffold, exert immunomodulatory effects in the host microenvironment, as well as differentiate into mature adipocytes. This has recently encountered a heightened interest within the Plastic Surgery community with the incorporation of adipose-derived stem cell rich content, stromal vascular fraction, into lipoaspirate for AFG of which early results have been encouraging especially in the realm of facial plastics and breast augmentation. Yet, certain concerns remain regarding this modality for reconstructing post-oncological defects. Are the long-term effects in terms of volume retention and graft survival superior to that of lipofilling alone? Are there potential side-effects of adipose-derived stem cell constituents which may confound radiographic imaging results and interpretation such as that in mammography? Is this technique proven to be oncologically safe in terms of locoregional recurrence, disease relapse or systemic metastases? This article aims to outline the facts surrounding the enigmatic subject of adipose-derived stem cell therapy and non-vascularized fat grafting based on prevailing evidence, and provide meaningful discourse regarding the necessity of adipose-derived stem cell therapy, particularly with high-stakes conditions such as post-oncologic reconstruction.

Current state of autologous fat grafting and its clinical applications

Since the inception of Coleman's technique for structural fat grafting in 1997, where fat tissue was harvested manually with 3 mm blunt cannulas and 10 ml syringes before proceeding to centrifuge the fat, AFG has enjoyed improved graft retention rates and a consequence, a surge in popularity.[3] In part, this may be attributed to less traumatic handling of the grafts which reduces the risk of adipocyte cell death through maintenance of its membrane integrity. Further, the centrifugation process has been shown to be particularly important because it condenses the fat by removing contaminating substances such as oil and red blood cells, which potentially reduce the viability of the engrafted fat. Lastly, by placing minimal amounts of grafted fat in multiple passages/tunnels within the subcutaneous tissue, there is maximal contact between the host tissue and graft effectively enhancing plasmatic imbibition and diffusion of essential nutrients.

As a tool for soft tissue reconstruction, AFG is now indicated for a multitude of clinical applications, including that of chronic wounds, post-oncological reconstruction, aesthetic surgery, trauma and burns. This exploits its characteristics as an ideal filler on the premise that it is autologous, completely biocompatible, naturally integrates with host tissues, removable if necessary, and potentially permanent.[3] As described in Piccolo and colleagues' impressive clinical case series, they harnessed AFG on the basis of its metabolic and regenerative properties of increasing vascularization and improving tissue regeneration and remodeling for burns, vascular wounds and scars which effectively decreased the amount of hypertrophy, fibrosis and increased scar malleability.[4] For the ageing and atrophied face, AFG renders enhanced volumetric rejuvenation by naturally integrating with the facial tissues, and arguably produces more natural-appearing, youthful, sustained and long-lasting effects as compared to synthetic fillers.[5] AFG has traditionally been regarded as a taboo subject within field of breast cancer reconstruction in view of a theoretical risk of adipose-derived stem cells within the fat contributing to tumor recurrence. These fears have recently been shown to be unfounded based on a 719-patient matched controlled study conducted by the MD Anderson Cancer Center. Their results showed that lipofilling for breast cancer reconstruction post-resection did not contribute to an increase in locoregional recurrence, systemic recurrence or a second breast cancer as compared to the control group.[6] This finding are affirmed by a meta-analysis performed by Agha et al. which showed that there are no significant oncologic ramifications of AFG versus traditional reconstructive methods after pooling data from 3624 patients.[7] Apart from the breast, AFG has notably been used to reconstruct post-oncologic defects within the head and neck[8,9] although this must be acknowledged that the literature only consists of case series, and a larger randomized control trial will be necessary to evaluate oncologic safety.

Although the risks are significantly lower than other more extensive reconstructive options, there remain certain complications to this procedure. A recent systematic review by Yu and colleagues has demonstrated that of 596 patients studied, the survival rate of fat grafts varied from 34 to 82% in the breast and 30–83% in the face.[10] The American Society of Plastic Surgeons Fat Grafting taskforce further reports that though not unduly high, potential complications include that of infection, bleeding, less than expected beneficial outcomes based on patient perceptions as well as possible interference with breast cancer detection, which may necessitate biopsies to distinguish microcalcifications from actual tumors.[11]

Adipose-derived stem cells and stromal vascular fraction – clarifications on terminology, characteristics and preparation

For the purposes of discussion, it will be pertinent to first address the following definitions, according to the International Federation for Adipose Therapeutics (IFATS).[12] A stem cell is characterized by its ability to self-renew and multipotency. A progenitor cell has limited proliferation potential but is still able to differentiate into one or several specific cell types. Stromal cells are connective tissue cells of any organ. Although often used interchangeably, adipose-derived stem cells (ASCs) and stromal vascular fraction (SVF) are distinct but associated entities within the field of regenerative medicine, each having different inherent attributes. SVF consists of a heterogenous mesenchymal population of cells, which comprise of 4 distinct populations based on their cell-surface markers upon performing flow cytometry.[13] These include: (a) CD45+ haematopoietic cells (leukocytes); (b) CD31+/CD34+/CD45− vascular endothelial cells; (c) CD31−/CD34+/CD45− adipose-derived stromal/stem cells (ASCs); and (d) CD31−/CD34−/CD45− other cells which consist of vascular pericytes

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