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The Role of Stem Cells in Aesthetic Surgery: Fact or Fiction?

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Abstract

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Stem cells are attractive candidates for the development of novel therapies, targeting indications that involve functional restoration of defective tissue. Although most stem cell therapies are new and highly experimental, there are clinics around the world that exploit vulnerable patients with the hope of offering supposed stem cell therapies, many of which operate without credible scientific merit, oversight, or other patient protection.

We review the potential, as well as drawbacks, for incorporation of stem cells in cosmetic procedures. A review of FDA-approved indications and ongoing clinical trials with adipose stem cells is provided. Furthermore, a “snapshot” analysis of websites using the search terms “stem cell therapy” or “stem cell treatment” or “stem cell facelift” was performed.

Despite the protective net cast by regulatory agencies such as the FDA and professional societies such as the American Society of Plastic Surgeons, we are witnessing worrying advertisements for procedures such as stem cell facelifts, stem cell breast augmentations, and even stem cell vaginal rejuvenation. The marketing and promotion of stem cell procedures in aesthetic surgery is not adequately supported by clinical evidence in the majority of cases.

Stem cells offer tremendous potential, but the marketplace is saturated with unsubstantiated and sometimes fraudulent claims that may place patients at risk. With plastic surgeons at the forefront of stem cell-based regenerative medicine, it is critically important that we provide an example of a rigorous approach to research, data collection, and advertising of stem cell therapies.

Keywords: Stem Cell Facelift, Rejuvenation, Breast Augmentation, Cell-Assisted Lipotransfer

Introduction

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Cosmetic surgery is a lucrative business, with $11 billion spent on cosmetic procedures in the United

States in 2012 (1). Over the past decade, the demand for cosmetic procedures has increased. This is likely due to a combination of an aging population, a desire to retain youthful looks, growing social acceptance of cosmetic procedures, and the availability of minimally-invasive options. According to the American Society of Plastic Surgeons 2012 report, the number of cosmetic procedures performed by its members over the past year was 14.6 million, up 5% from 2011(1). Interestingly, there has been an increase in the number of minimally-invasive procedures performed, and a decrease in the number of surgical procedures being performed (1). Facial procedures saw the most growth in 2012 (1).

A shift towards more minimally-invasive techniques has resulted in a wider range of practitioners performing cosmetic procedures (2). Along with plastic surgeons, these include dermatologists, family medicine practitioners, anesthesiologists, and ophthalmologists (3). A worrying trend is the rise in the number of non-surgery-trained individuals providing surgical cosmetic treatments, especially liposuction (4). This trend has challenged the traditional practice of plastic surgery, and resulted in the emergence of a corporate medicine model, where the public is bombarded with the promotion of trademarked procedures/devices and advertising that promises stunning results, with claims of innovation, superiority, and improved safety (5). Operations that once included detailed history and physical examinations, along with lengthy consultations are being threatened by the commoditization of cosmetic procedures, with sales people who tell prospective patients what “work” they need done (6).

Another worrying aspect of unregulated stem cell clinics is that practitioners, ranging in expertise from plastic surgeons to obstetricians, along with other specialists are treating conditions that they would not encounter in their normal clinical practice, such as Parkinson’s disease. This is an unrealistic, and potentially dangerous use of adult stem cells. While the potential of ASCS to differentiate into neurons has been established in vitro and in a few in vivo studies there is still insufficient evidence to justify their use clinically (7). Spontaneous differentiation of adipose-derived stromal cells into therapeutic cell types for Parkinson’s disease is biologically unrealistic (8). Injecting immature stem cells does not provide a long-term treatment for Parkinson’s disease, and the risk associated with uncontrolled growth of transplanted cells is unacceptable (8).

In line with this recent shift in marketing practice has been the emergence of stem cell-related therapies. Stem cell therapy, however, remains in its infancy, but there are a growing number of cosmetic practitioners that are advertising minimally invasive, stem cell-based rejuvenation procedures. With unsubstantiated claims that these procedures are safer, have equivalent or better outcomes, and faster recovery periods than conventional procedures, many of these practitioners are emphasizing profit over quality and safety. Importantly, the emergence of innovative advances in cell-based therapies requires the same rigor in experimental testing that is required for all other medical therapies to ensure the safety and education of our patients.

Stem cells

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Stem cells have captured the imagination of many due to deeper insights into the biology of cells they provide, as well as potential for treatment of many diseases. Stem cells are functionally defined by their ability to self-renew and to generate differentiated progeny cells with more restricted potential (9). The role of stem cells changes significantly throughout life, as stem cells must alter their properties to match the changing growth and regeneration demands. Reflecting these changing roles, there are many different types of stem cells which have been defined. Pluripotent stem cells, such as embryonic or induced pluripotent stem cells, have the capacity to generate tissue from any of the three germ layers (10, 11). Their clinical use, however, has been hampered by risks for teratoma formation and, in the case of embryonic stem cells, ethical concerns (12). Multipotent stem cells, such as mesenchymal stromal cells (MSCs), lack these shortcomings, but have the capacity to differentiate into a more limited number of closely related cells (13, 14). Finally, unipotent stem cells, while retaining the ability to self-renew, can only produce one cell type. This last class, while having limited utility in

regenerative strategies, is intimately involved in normal tissue homeostasis at a wide variety of sites including skin, lung, liver, and intestinal lining (15–18).

Of these different types of stem cells, of particular clinical interest are the MSCs. MSCs have the capacity to differentiate into bone, cartilage, muscle, and fat. While the best-characterized MSC is the bone-marrow derived MSC, their clinical utility is limited as isolation of these cells is associated with considerable donor site morbidity and low yield. However, Zuk and colleagues identified a similar cell type with greater ease of harvest and higher yield in mature adipose tissue which also possessed multilineage potential (13). Importantly, the stromal vascular fraction (SVF) from which these adipose-derived stromal cells (ASCs) are derived is highly heterogeneous, and also contains an array of other cell types including endothelial cells, pericytes, fibroblast, leukocytes, hematopoietic stem cells, and endothelial progenitor cells (19). While a comprehensive profile of antigen expression has yet to be established for ASCs, studies have characterized these cells within the SVF by the following antigen profile: $CD45^{-}$, $CD235a^{-}$, $CD31^{-}$, $CD34^{+}$, $CD106^{-}$, and $CD36^{+}$ (20). In general, their abundance and relative ease of harvest along with their autogenous immune-privileged status as a result of human leukocyte antigen-DR expression have made them into an attractive candidate for regenerative therapies (21).

The most notable area of aesthetic surgery where ASCs may be applicable is in autologous fat grafting. Autologous fat grafting has become popular for soft tissue augmentation throughout the entire body (22, 23). There is, however, much variability in the literature regarding the high resorption of fat grafts (24). These disappointing and unpredictable outcome data provided the impetus for developing strategies for improving fat graft survival. One such strategy is cell assisted lipotransfer (CAL) where the stromal vascular fraction containing ASCs is isolated from a portion of the aspirated fat and then recombined with the remaining fat prior to injection (25). Interestingly, Yoshimura and colleagues reported that they were able to achieve stable augmentation of 100–200 mL using CAL after a mean fat injection of 270 ml in patients undergoing cosmetic breast augmentation (25). Similarly, enrichment of fat grafts with ASCs was also reported to enhance volume retention following injection into the upper arm (26). This strategy, however, remains controversial, as a comparative clinical study reported no significant difference in fat graft retention between CAL and water assisted lipotransfer for breast augmentation (27). Although holding tremendous promise, the clinical use of ASCs in aesthetic surgery is thus still in its infancy. It is therefore vital that clinical practice should be guided by critical evaluation of the data, ideally in level one evidence studies, rather than anecdotes, word of mouth, or attention-grabbing headlines.

As has been previously noted by colleagues in the plastic surgery community, it is also vitally important to use appropriate terminology and take care not to confuse traditional autologous fat grafting with therapies that specifically use ASCs (28). In order not to mislead the public, it will be important to distinguish between simple soft tissue volumetric augmentation of the face using standard fat grafting versus fat grafts enriched with ASCs. It is also important not to use potentially confusing terminology like “stem cell facelift” to describe procedures that are nothing more than volumetric lipofilling with or without ASC enrichment (29).

With every new scientific advancement, it is the responsibility of scientists and physicians to guide and educate the public on the advantages and disadvantages of any proposed therapy. Overstating potential benefits based on early and incomplete evidence can only serve to erode the public’s trust in the medical profession and, more concerning, compromise the safety of our patients. For example, there is still some uncertainty in the literature regarding the ability of ASCs to generate certain lineages *in vivo* (30). Furthermore, there have been conflicting reports in the literature regarding the potential for ASCs to promote or inhibit tumorigenesis (31–36). Further areas of concern regarding ASCs in aesthetic surgery relate to the possible use of non-autologous cells in countries outside of the USA. These cells should be used in an autologous fashion to minimize any immunologic consequences as a result of

self/non-self identity. Finally, the use of stem cells in aesthetic procedures, not unlike other non-aesthetic indications, opens up the possibility of medical tourism and misrepresenting therapeutic benefits to attract patients.

Nevertheless, it is clear that ASCs have the potential to play an important role in both regenerative medicine and cosmetic surgery. Rohrich *et al.* reported that by 2012, of the 174 published cases of patients treated with ASCs and 121 patients enrolled in clinical trials in the plastic surgery literature, no major adverse effects were noted (37). While encouraging, it is essential that plastic surgeons proceed with caution and only after close scrutiny of the hard evidence. Standard protocols for the use of these cells must still be developed such as optimal numbers of ASCs to be used per treatment. To that end, the American Society for Plastic Surgeons and the American Society for Aesthetic Plastic Surgery have commissioned task forces to develop position statements built on the best available data (38) These attempts to provide a unified and coherent approach based on up-to-date data must be commended.

Direct-to-consumer marketing of cosmetic stem cell therapies

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Given the potential for stem cells and burgeoning interest for incorporation of these cells in various cosmetic procedures, we therefore characterized the direct-to-consumer marketing of stem cell medicine through a content analysis of corporate websites obtained by a Google search (www.google.com) using the search terms “stem cell therapy” or “stem cell treatment” or “stem cell facelift” in November of 2013. This “snapshot” of 50 cosmetic clinics offering “stem cell” treatment reflects the current state of marketing and is analyzed in Figure 1. The use of the “stem cell” label was taken at face value, and despite adopting this approach in the following analysis, we have no knowledge of the true quality of stem cells used. Due to the heterogeneity of isolated cell populations, particularly in fat, and an inability of these practitioners to sort the cells by flow or magnetic cytometry, it is likely that the cells used by these clinics, as elaborated above, contain a host of other cells in addition to fat-derived stromal cells.

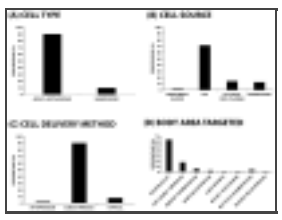

Figure 1

Nature of stem cell therapies offered across surveyed websites

In addition, numerous clinics were found to offer platelet-rich plasma (PRP) treatments which they marketed as stem cell treatment. Of note, PRP does not contain stem cells and is rather autologous plasma that is enriched with platelets (39). Indeed, platelets by their very nature are cell fragments, and technically do not even come under the umbrella term of cells as they lack a cell nucleus. Nonetheless, PRP has found application in a range of clinical scenarios such as orthopedics, ophthalmology, and wound healing, serving as a growth factor pool for improving tissue regeneration (40). However, to market PRP as a stem cell therapy is misleading.

FDA-Approved personalized cell therapy in cosmetic surgery

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As use of stem cells in cosmetic medicine continues to expand, it is important to note that FDA approval remains limited. In June of 2011, after almost 10 years of review, the US Food and Drug Administration (FDA) approved laViv (azficel-T), a first-in-class personalized cell therapy for eliminating fine wrinkles or nasolabial folds around the nose and mouth (41). Each laViv treatment involves harvesting a patient’s own fibroblasts from behind the ear, culturing them for 90 days, and then reinjecting expanded cells into the dermis during a series of treatments (41). The company’s safety data were sufficient to warrant approval, but because laViv is so novel, approval was contingent on extensive post-market surveillance for immune effects and skin cancer (41).

A search for “adipose stem cells” on the clinicaltrials.gov website yielded 109 results. However, only a

small proportion of these clinical trials focus on cosmetic treatments. Studies that do focus on cosmetic procedures include trials to establish the role of ASCs in volume retention of fat grafts, improving fat graft retention in the breast following breast cancer resection, reducing wrinkles when co-delivered with fat grafts, skin ulcers, diabetic wounds, and improving skin quality of irradiated breasts. In addition, one study is presently looking at the role of ASCs to improve osteogenesis in composite tissue grafts and another is looking at the role of ASC-enhanced fat grafts following craniofacial trauma.

Inherent risks of cell processing

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When considering clinical use of stem cells, one must be cognizant of the fact that cell and tissue processing pose a risk of contamination and/or damage to cells. Regulation of stem cell therapy is thus paramount to ensure patient safety. For this reason, the growing number of "stem-cell based" cosmetic procedures is worrisome, due to the lack of oversight and dearth of scientific studies or trials to evaluate their efficacy and safety *in vivo*.

Potential contamination of and damage to cells becomes an issue when cell-based products involve more than minimal manipulation, including cell expansion in culture and differentiation (42). In theory, cells removed from a patient and replaced during the same surgical procedure pose no greater risk of disease transmission than the surgery itself (42). However, cell culture typically involves the use of nonhuman serum, usually obtained from fetal calves, and therefore introduces a potential risk for prion infection (43). In light of this, current FDA guidelines specify that fetal-calf serum must come from a country certified to be free of this disease. Additionally, cell expansion *in vitro* may also involve the use of xenogenic feeder cells, particularly in the case of human embryonic stem cells. This also poses a potential risk of infectious disease transmission.

Another safety concern revolves around malignant stem cell transformation. Stem cells have clear similarities to cancer stem cells, and it has been demonstrated that mesenchymal stromal cells can undergo spontaneous malignant transformation following long-term *in vitro* culture (44). Despite the enormous potential for stem cells demonstrated in preclinical testing, it is thus essential to recognize and appreciate both the promise and limitations for use of stem cells in clinical therapeutics (45).

Skin Anti-Aging Therapies

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Anti-aging therapies seek to delay degeneration of the skin and its support system. As aging proceeds, reduced skin elasticity secondary to changes in skin thickness and collagen organization and solar elastosis results in skin folds and wrinkles (46, 47). Extrinsic effects such as photoaging also contribute significantly to changes in skin aesthetics through the induction of irregular pigmentation, dyschromia, and wrinkles (46, 48). It is important to bear in mind that the mechanisms behind aging are cellular and molecular in nature, and therefore any therapy claiming to have anti-aging effects must directly impact these mechanisms. In this regard, although volumetric enhancement often results in a more youthful form and appearance, it does not represent a true anti-aging therapy for this reason.

Collagen remodeling represents an effective target for anti-aging therapies. Laser treatment can induce collagen remodeling by promoting synthesis of both type I and III collagen (49, 50). In addition to laser treatment, cytokines and growth factors can impact collagen remodeling through their effects on dermal fibroblasts. Given the ability of cytokines such as vascular endothelial growth factor, platelet-derived growth factor, and transforming growth factor-β to promote collagen synthesis and turnover, stem cells capable of producing these factors may hold promise for anti-aging therapies. The ability of ASCs to produce an array of cytokines therefore makes them a candidate for anti-aging therapies. However, the evidence to support the anti-aging effects of stem cells remains minimal at best.

Relatively few studies on ASCs and other stem cells have demonstrated what could be considered a true anti-aging effect. One such study claimed that ASCs minimized the appearance of UVB-induced

wrinkles in mice through the activation of dermal fibroblasts by secreted factors (51). More often than not, however, improved facial and skin aesthetics are achieved through enhanced volumetric rejuvenation by transplanted cells. Rather than a true "stem cell facelift" where transplanted cells exert prolonged anti-aging effects, these procedures amount to stem cell-enriched lipofilling, a well-known and established technique.

Such criticism is not meant to minimize the efficacy of such therapies for creating a more youthful appearance. There is certainly room for improvement within the field of volumetric rejuvenation, and biomaterials/molecules designed to provide an optimal environment for transplanted stem cells have recently emerged as a promising area of research. For example, autologous MSCs when combined with hyaluronic acid were able to fill in deep skin folds in the face, showing progressive improvement of skin tone and decreasing lines of expression (52). Slowing or even reversing the effects of aging thus requires a precise understanding of the molecular and cellular events involved in the aging process, events which may not be fully addressed by volume filling alone.

The effects of aging on stem cells

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Another important consideration to be made with incorporation of stem cells into cosmetic procedures is the effect of age on the cells themselves. Stem cells are not immune to the process of aging, and their function is tightly regulated by their surrounding environment known as the stem cell niche. The hematopoietic system provides the best evidence for the role local environment plays in guiding maintenance and differentiation of stem cell populations and the effects of aging on this balance. Studies have shown hematopoietic stem cells (HSCs) have reduced functional ability as the capacity to give rise to progeny cells becomes skewed towards the myeloid lineage due to transcriptional changes that occur with advanced age (53). Furthermore, aging is also associated with decreased competence of the adaptive immune system and an increased incidence of myeloid diseases, including leukemias (54, 55).

The functional decline of aged stem cells is due to a host of factors. These include both exogenous sources, such as genotoxic chemicals, UV irradiation, and ionizing radiation and endogenous sources such as a build-up of reactive oxygen species, telomere attrition, and stalled replication forks (56, 57). A series of experiments evaluating HSC reserves and functional capacity in young and old mice deficient in several different DNA-repair pathways demonstrated the impact of DNA damage on stem cell function (58, 59). With age, stem cells were found to accrue DNA damage, and depending on the nature and extent of this damage, mutagenic lesions arising in stem cells have the potential to drive cells to senescence, apoptosis, or tumor transformation (56, 58). Therefore, as aging has been associated with a cell-intrinsic decline in the regenerative potential of stem cells, claims of rejuvenation in aged individuals through transfer of cells become more dubious.

Conclusion

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Organized plastic surgery has embarked on a strategic initiative to incorporate principles of evidence-based medicine into all aspects of education, publication, training, certification, and practice (60–62). Currently, the marketplace is characterized by direct-to-consumer, corporate medicine strategies that are characterized by unsubstantiated, and sometimes fraudulent claims, that put our patients at risk. With plastic surgeons at the forefront of stem cell-based regenerative medicine, it is critically important that we provide an example of a rigorous approach to research, data collection, and advertising of stem cell therapies. Stem cells offer tremendous potential for cosmetic applications, but we must be vigilant to avoid unscientific claims which may threaten this nascent field.

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Footnotes

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Data Presented in this manuscript have not been previously presented at any meeting

Financial Disclosure and Products Page

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

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