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Donor variability in adipose tissue-derived stem cells: implications for the clinical efficacy of autologous fat grafting

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Abstract

Autologous fat grafting is a common technique in cosmetic and reconstructive surgery, addressing facial rejuvenation, breast contouring, scar mitigation, and soft tissue corrections. However, clinical outcomes can be inconsistent and unpredictable. While extensive research has explored the mechanisms of harvesting, purifying, and transplanting adipose tissue, there is a notable gap in understanding the impact of donor-related factors on fat grafting success. This review aims to fill this gap by examining how variables like donor age, sex, health status, and anatomical site of fat harvest influence the biological efficacy of adipose-derived stem cells (ASCs). Younger donors often exhibit higher ASC proliferation rates and regenerative potential, while older donors may have reduced cell viability. Hormonal differences between sexes and donor health conditions, such as obesity or diabetes, can also impact ASC functionality and graft outcomes. The anatomical source of the fat further affects its cellular composition and regenerative potential. Understanding these donor-related factors is vital for optimizing fat grafting techniques. The review also explores innovative strategies, such as adipose tissue cryopreservation and acellular fat matrices, to mitigate donor variability. These approaches offer promising avenues for enhancing the predictability and effectiveness of fat grafting. By synthesizing current knowledge and highlighting novel strategies, this review aims to improve clinical outcomes and advance the field of aesthetic and reconstructive surgery.

Keywords

Fat grafting, donors, adipose-derived stem cells, biological function, clinical outcomes, regenerative medicine, cosmetic surgery, reconstructive surgery

Introduction

Autologous fat grafting has garnered considerable attention in both cosmetic and reconstructive surgery due to its numerous advantages, including abundant availability, procedural simplicity, favorable

postoperative outcomes, and minimal risk of rejection. This technique has found diverse applications, from facial rejuvenation and breast shaping to scar treatment. Despite its widespread use, the clinical efficacy of fat grafting remains inconsistent, with reported retention rates within the first year ranging from 10% to 80% [1]. This variability in outcomes poses a significant barrier to the broader adoption of fat grafting in clinical practice. A substantial body of research has been dedicated to understanding the regenerative mechanisms involved in adipose tissue processing and transplantation. These studies have focused on optimizing harvesting techniques, improving cell survival, and enhancing the overall integration of grafted fat into recipient sites. However, the influence of donor-related factors on the outcomes of fat grafting has been relatively understudied and poorly documented. The limited literature available fails to provide a comprehensive overview of how donor characteristics impact the functional properties of adipose tissue-derived stem cells (ASCs), which are crucial for the success of fat grafting procedures [2].

This review aims to fill this gap by examining the mechanism of action of ASCs and systematically evaluating the effects of donor-related factors on the biological functions of adipose tissue and ASCs. By synthesizing existing research findings, we aim to elucidate how variables such as donor age, sex, health status, and anatomical site impact the survival, integration, and long-term stability of fat grafts. Understanding these donor-related factors is essential for optimizing fat grafting techniques, enhancing clinical outcomes, and facilitating the wider acceptance and utilization of this valuable procedure in cosmetic and reconstructive surgery. Donor age is one of the critical factors that can significantly influence the properties of ASCs. Younger donors typically have a higher proliferation rate and greater regenerative potential, which may translate to better graft retention and integration. Conversely, ASCs from older donors may exhibit reduced viability and differentiation capacity, potentially leading to lower graft survival rates. Similarly, donor sex may also play a role, with some studies suggesting that female donors' ASCs might differ in their functional properties compared to those from male donors. This could be due to hormonal differences that affect the cellular environment and regenerative capabilities (Table 1).

Health status is another crucial donor-related factor. Donors with metabolic conditions such as obesity or diabetes may have ASCs with impaired functionality, affecting the overall success of fat grafting. The presence of systemic inflammation or other chronic diseases can alter the microenvironment of adipose tissue, thereby influencing the quality and regenerative potential of the harvested ASCs. Furthermore, the anatomical site of fat harvesting can impact the characteristics of ASCs. Fat obtained from different body regions may vary in cellular composition, vascularity, and stem cell content, all of which are essential for graft viability and integration.

By addressing these critical aspects, this review seeks to provide a comprehensive understanding of donor variability in ASCs and its implications for the clinical efficacy of autologous fat grafting. By identifying and mitigating the factors that contribute to variability in clinical outcomes, we aim to pave the way for improved practices and patient outcomes in this field. The insights gained from this review could also inform the development of standardized protocols for fat grafting procedures, ultimately enhancing the predictability and success of this versatile surgical technique.

The mechanism of action of ASCs

ASCs are derived from a heterogeneous cell population known as the stromal vascular fraction (SVF), which is enzymatically extracted from subcutaneous adipose tissue obtained during procedures like liposuction to remove excess fat. The SVF is then centrifuged, and the cells are cultured in flasks, leading to a relatively homogeneous population of spindle-shaped, fibroblast-like cells known as ASCs after several passages [3]. The quality of ASCs is evaluated based on their self-renewal capacity, proliferation rate, and multi-lineage differentiation potential. Techniques such as flow cytometry, colony-forming unit (CFU) assays, and differentiation assays are used to assess their stemness. ASCs express mesenchymal lineage markers like CD90, CD73, CD105, and CD44, but do not express hematopoietic markers such as CD45 and CD14, nor the endothelial marker CD31. Because ASCs lack expression of the human leukocyte antigen-DR isotype (HLA-DR) on their surface, they are considered relatively immune-privileged, making them a viable treatment option for graft-versus-host disease (GvHD) patients [4–6]. Unlike bone marrow-derived mesenchymal

Table 1. Overview of major considerations in fat grafting: from harvesting to placement in the recipient site

Stage	Key issues	Details
Donor selection	Donor age	Younger donors may have higher proliferation rates and regenerative potential
	Donor sex	Potential hormonal influences affecting adipose tissue-derived stem cell (ASC) functionality
	Donor health status	Conditions like obesity, diabetes, and systemic inflammation can impair ASC functionality
	Anatomical site of fat harvesting	Variability in cellular composition, vascularity, and stem cell content based on the harvest site
Fat harvesting	Technique	Methods such as liposuction technique (manual vs. power-assisted) can impact cell viability
	Harvest site	Different body areas may yield varying quality and quantity of ASCs
Processing	Isolation of ASCs	Techniques for isolating ASCs from fat can affect the viability and functionality of the cells
	Purification methods	Methods like centrifugation or filtration can influence the quality of the graft
	Additives and enhancements	Use of growth factors, platelet-rich plasma (PRP), or other additives to improve graft outcomes
Graft preparation	Volume of fat	The amount of fat prepared for grafting can impact integration and survival
	Cell concentration	The optimal concentration of ASCs within the graft is crucial for success
Placement technique	Injection technique	The method of injecting fat (e.g., microdroplet, linear threading) affects distribution and survival
	Layering and integration strategy	Proper layering techniques to promote vascularization and integration
Postoperative care	Monitoring and follow-up	Regular monitoring to assess graft survival and integration
	Management of complications	Addressing issues such as fat necrosis, cyst formation, and infection
	Optimization of patient health	Ensuring optimal patient health to support graft survival and integration
Long-term outcomes	Graft retention rates	Variability in retention rates ranging from 10% to 80% within the first year
	Assessment of functional and aesthetic results	Evaluating both the functional improvement and aesthetic enhancement over time
	Impact of donor-related factors	Long-term studies on how donor characteristics influence outcomes

stem cells (BM-MSCs), ASCs express the fatty acid translocase marker CD36 and do not express the cell adhesion marker CD106 [7, 8].

ASCs have been shown to differentiate into mesodermal lineages, including adipocytes, osteoblasts, chondrocytes, and myocytes, both in vitro and in vivo. Methods to confirm differentiation include the expression of specific genes and flow markers for each lineage, special staining techniques, and quantitative analysis [9, 10].

Additionally, ASCs can differentiate into non-mesodermal lineages such as endothelial cells, hepatocytes, neurons, pancreatic cells, and cardiomyogenic cells. Although it is not thoroughly documented whether ASCs can effectively differentiate into non-mesodermal lineages, it is believed that their heterogeneity and expression of progenitor stem-cell markers enable this differentiation. CD34 is thought to facilitate the trans-differentiation of ASCs into endothelial cells, cardiomyocytes, neurons, and hepatocytes [11, 12]. Cao et al. [13] demonstrated that ASCs could differentiate into endothelial cells when cultured with vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) in vitro. The presence of endothelial markers such as CD34, PECAM, and VE-cadherin in treated cells indicated potential differentiation into functional endothelial cells. This finding was supported by an in vivo experiment where ASCs injected into the tail vein of ischemic nude mice differentiated into functional endothelial cells, contributing to neovascularization, as evidenced by CD34 expression. Yin et al. [14] showed that ASCs could differentiate into functional hepatocyte-like cells in vitro and in vivo by adding FGF, hepatocyte growth factor (HGF), and epidermal growth factor (EGF) to the culture media. The functionality of these

hepatocyte-like cells was confirmed by positive immunostaining for hepatocyte-specific markers like albumin (ALB) and alpha-fetoprotein (AFP), as well as periodic acid-Schiff stain (PAS) staining for glycogen storage. Adding trichostatin A (TSA) to the culture media further increased ALB expression in differentiated ASCs.

The differentiation of ASCs into cardiomyocyte-like cells (CLCs) was investigated by Zhu et al. [15], who found that both direct cell-to-cell contact and indirect co-culture with cardiac cells induced differentiation, marked by high expression of troponin-I (TnI), myosin heavy chain (MHC), and connexin43 in vitro. Another study by Kakkar et al. [16] suggested that ASCs could differentiate into functional CLCs more effectively than BM-MSCs in vitro when induced with transforming growth factor beta 1 (TGF-β1), as evidenced by MHC and TnI expression and increased intracellular calcium levels in ASC-induced cells. However, several parameters, including the co-culture system, soluble factors, and specific conditions, need further exploration before CLCs can be used in in vivo heart transplants. Brzoska et al. [17] showed that ASCs could differentiate into epithelial cells in vitro when treated with all-*trans* retinoic acid (ATRA), as proven by the expression of cytokeratin 18 (CK18), an epithelial marker. Griesche et al. [18] enhanced in vitro differentiation of ASCs into epithelial cells by adding ATRA, Activin A (ActA), and bone morphogenetic protein-7 (BMP-7) to the culture media, confirming the results with the expression of zonula occludens protein 1 (ZO-1) and CK18 in treated cells. However, more research is needed to explore the potential use of ASC-derived epithelial cells in organ injury repair.

Thus, specific progenitor stem-cell markers and culture conditions can induce ASC differentiation into multiple cell types. However, it is important to confirm the functionality of differentiated ASCs, the reproducibility of results, and their application in regenerative medicine. Additionally, the adipose tissue depot used for ASC isolation impacts their biological properties. ASCs harvested from subcutaneous fat in the abdomen and thigh show similar proliferation rates and multi-differentiation potential [19]. Studies have shown that subcutaneous ASCs (S-ASCs) have a higher proliferation rate and differentiation capacity towards adipocytes and chondrocytes, but lower osteogenic potential compared to visceral ASCs (V-ASCs). Despite differences in gene expression and differentiation potential, both S-ASCs and V-ASCs have been shown to be beneficial in treating heart failure [20]. S-ASCs, however, have proven more effective in treating osteoarthritis due to their immunosuppressive ability to decrease the expression of inflammatory genes [21]. Compared to BM-MSCs, ASCs exhibit higher differentiation capacity, proliferation rate, and regenerative potential. Zhu et al. [22] found that ASCs maintain their multipotential differentiation ability up to passage 25.

Adipose tissue includes adipocytes, ASCs, extracellular matrix, macrophages, muscle cells, and other cellular components, among which ASCs play a vital role in the clinical efficacy of adipose tissue. Although the exact mechanism of ASCs is unclear, they may be related to the cytokines secreted by ASCs, such as VEGF, fibroblast factor-2, interleukin-10 (IL-10), matrix metalloproteinases, EGFs, etc. Brongo et al. [23] reported that ASCs secrete cytokines such as VEGF and TGF-β, and histological staining showed that these cytokines improve scar skin texture by promoting new collagen deposition, local angiogenesis, and dermal papilla regeneration. Borovikova et al. [24] found that activated ASCs could reduce the expression level of TGF-β4 by regulating the TGF-β/Smad signaling pathway, thereby reducing the abnormal deposition of collagen and the proliferation and differentiation of fibroblasts. On the other hand, ASCs reduce collagen fibrillar production and aggregation by inhibiting the p1/MAPK signaling pathway [25]. Strong et al. [26] confirmed that the expression levels of cyclooxygenase-6 and prostaglandin E-2 increased after ASC transplantation, while the expression of CD2+ and CD4+ T lymphocytes decreased, further demonstrating that ASCs can inhibit scar formation by regulating immune and inflammatory responses.

Donor factors

Age

It has been reported that the proliferation and differentiation ability of ASCs decreases with age [27]. On the one hand, this may be related to the reduced sensitivity of preadipocytes to extracellular signaling

responses; on the other hand, hypoxia in aging adipose tissue leads to excessive cytokine secretion by ASCs, and overexpression of tumor necrosis factor-α (TNF-α) and IL-6 will activate neighboring cells into an inflammatory state, resulting in stunted adipocyte production and enhanced lipolysis [28]. Alt et al. [27] compared ASCs in the younger group (< 20 years) and the older group (> 50 years) and showed that age was significantly negatively correlated with the proliferation and differentiation ability of ASCs. Choudhery et al. [29] found that osteogenic potential decreased significantly with age, but there was no statistically significant difference in adipogenic potential. Harris et al. [30] divided the patients into two groups, > age 70 years and < 70 years, and they did not find a significant correlation between ASC proliferation and differentiation and age. Oranges et al. [31] performed fat grafting on three mice of different age groups, namely 11 weeks old, 3 months, and 3 years old (equivalent to human prepuberty, middle-aged, and elderly, respectively), and reconstructed the three-dimensional images of graft volume with time by CT after surgery, and further confirmed that the fat grafting rate of mice in the 6-week-old group was higher than that in the 1-year-old group by histological testing. Currently, most investigators still support a negative correlation between age and ASCs, which provides clinicians with important information that fat grafting may be better at a young age.

Gender

The influence of gender on the biological function and therapeutic potential of ASCs is an emerging area of interest, but current understanding remains limited and somewhat inconclusive. While clinical studies directly correlating gender with human ASC production are lacking, some preclinical research provides insights into potential gender-related differences in ASC function.

Gender differences in adipogenesis

Higher adipogenic potential in females—research by Ogawa et al. [32] demonstrated that the expression level of peroxisome proliferator-activated receptor γ2 (PPAR-γ2), a critical marker for adipogenesis, was significantly higher (2.89 times) in female mice compared to male mice. PPAR-γ2 plays a crucial role in the differentiation of pre-adipocytes into adipocytes, suggesting that female ASCs might have a higher capacity for adipogenic differentiation. This finding implies that women may experience a higher retention rate of transplanted fat following fat grafting procedures than men, potentially due to more robust adipogenic activity.

Gender differences in osteogenic differentiation

Enhanced osteogenic potential in males—the studies by Aksu et al. [33] and Bragdon et al. [34] suggest a gender-related difference in the osteogenic differentiation potential of ASCs. Aksu et al. [33] conducted a study on ASCs derived from the abdominal fat of six patients of different genders and found that male ASCs exhibited a superior potential for osteogenic differentiation compared to female ASCs. This was consistent with findings from Bragdon et al. [34], which also indicated that male ASCs might be more predisposed to osteogenic differentiation. This difference could partially explain the higher incidence of osteoporotic fractures in women, as their stem cells might be less efficient in contributing to bone regeneration and repair.

Implications and need for further research

Lack of comprehensive understanding—while the above studies provide preliminary insights into how gender might influence ASC function, the current body of research is neither comprehensive nor definitive. The studies are limited by small sample sizes and the use of animal models or specific subpopulations, which may not fully capture the complexities of human physiology. Additionally, these findings may be influenced by other confounding factors such as hormonal levels, age, and underlying health conditions, which also differ between genders.

The observed gender differences in ASC function could be attributed to hormonal influences, such as estrogen and testosterone, which are known to play significant roles in adipose tissue distribution, metabolism, and cellular differentiation pathways. Estrogen, for example, is known to influence bone

density and fat distribution, which might partially explain the differences in ASC adipogenic and osteogenic potentials between genders.

The impact of gender on the biological function of ASCs remains an area requiring more focused research. The available evidence suggests there may be inherent gender differences in ASC function, particularly concerning adipogenic and osteogenic differentiation potentials. However, more comprehensive clinical studies with larger, diverse populations are needed to elucidate the full extent of these differences and their implications for ASC-based therapies. Understanding these gender-specific variations will be crucial for optimizing the therapeutic applications of ASCs in regenerative medicine and ensuring personalized and effective treatment strategies.

Underlying diseases

Impact of diabetes on ASCs

Diabetes, particularly in a hyperglycemic environment, significantly impacts the biological function and therapeutic potential of ASCs. Here's a summary of the findings from various studies:

Weakened functionality in diabetic microenvironment—diabetic ASCs (dASCs) often exhibit reduced functionality in hyperglycemic conditions. Kočí et al. [35] observed that dASCs from ischemic limbs of diabetic patients showed a high expression of fibroblast markers and a decreased expression of VEGF and osteogenic differentiation markers. This alteration may reduce the effectiveness of dASCs in wound healing therapies.

Potential for wound healing—despite the weakened state, some studies indicate that dASCs retain a capacity to promote wound healing. Zografou et al. [36] demonstrated that autologous dASCs injected into diabetic mice could enhance wound angiogenesis and epithelialization by secreting growth factors like TGF-β and VEGF, improving skin graft survival rates.

Variable therapeutic outcomes—contradictory findings have been reported regarding the therapeutic efficacy of dASCs. Cianfarani et al. [37] noted reduced proliferation and migration of dASCs, questioning their effectiveness in treating diabetic wounds. Similarly, Kim et al. [38] found that normal ASCs had a higher wound healing rate than dASCs, highlighting the general impairment of dASC therapeutic potential in diabetic conditions.

Successful healing in specific contexts—Amini et al. [39] found that dASCs could effectively heal pressure ulcers in diabetic mice, promoting angiogenesis and nerve regeneration. Xiao et al. [40] also noted that dASCs, despite reduced proliferative and osteogenic differentiation abilities, could still promote angiogenesis, collagen deposition, and nerve regeneration, aiding in pressure ulcer healing.

Influence of donor characteristics—the inconsistencies in these studies might be attributed to differences in donor characteristics. In vitro studies have shown that modifying the culture environment, such as adding insulin, can enhance or restore ASC capabilities under diabetic conditions [41].

Impact of HIV on ASCs

HIV infection affects adipose tissue and its cellular components, leading to potential implications for ASCs:

Mitochondrial dysfunction and cellular damage—research indicates that HIV proteins can damage the mitochondrial structure and function in adipocytes and stromal vascular cells, impairing the cells' metabolism and overall functionality [42, 43].

Inflammatory responses and altered immune balance—HIV infection alters the balance of CD4+ and CD8+ T cells within adipose tissue, affecting macrophage activation and leading to local inflammation. This could potentially impair the regenerative and therapeutic capacities of ASCs [42].

Metabolic disruptions—HIV-related mitochondrial dysfunction leads to impaired fatty acid metabolism and accumulation of oxidative insufficiency products. This disruption alters adipokine secretion and reduces glucose uptake, which may further compromise the functional integrity of ASCs [44].

Impact of other underlying conditions

Non-significant effects of certain conditions—some conditions, such as total cholesterol, hypertension, and kidney disease, have not shown significant effects on the biological functions of ASCs [45]. This suggests that not all underlying conditions equally impact ASC function, and more research is needed to clarify these relationships.

The varying effects of underlying diseases like diabetes and HIV on ASC function highlight the need for personalized approaches in stem cell therapies. Understanding the specific impacts of each condition on ASCs is crucial for optimizing their therapeutic use. Future studies should continue to explore these relationships, considering donor health as a critical factor in grafting outcomes.

Body mass index

Studies have shown that the differentiation, proliferation, and angiogenesis of ASCs in obese individuals, particularly those with a body mass index (BMI) of > 30 kg/m^2, are reduced [46]. Because the cell volume of obese people is larger than normal, the relative lack of phosphoprotein on the surface of adipocytes may increase the fragility of cell membranes, thereby increasing the basal rate of lipolysis [47]. Obesity changes in adipose tissue inflammation are similar to age, obesity changes adipose tissue metabolism and endocrine function, resulting in increased release of fatty acids, hormones, and pro-inflammatory molecules, immunohistochemistry shows that the expression rates of mononuclear macrophages, TNF, inducible nitric oxide synthase (iNOS), and IL-6 are significantly positively correlated with adipocyte size and body weight, and participate in the activation of inflammatory pathways to produce local inflammation [48]. Mitterberger et al. [49] compared ASCs before and after bariatric patients in obese patients with ASCs in normal-weight people and found that bariatric surgery and long-term caloric restriction greatly altered the programming of ASCs, thereby reducing DNA damage and improving viability. In 2015, Pérez et al. [50] also showed that the differentiation and proliferation capacity of ASCs decreased with increasing BMI, and they found that obesity changed telomerase activity and DNA length, suggesting a decrease in ASCs' self-renewal ability and early apoptosis. However, some scholars have questioned that Geissler et al. [51] divided 24 women with different BMIs into two groups (BMI ≥ 25 kg/m^2 or < 25 kg/m^2) and did not find an association between BMI and ASCs yield or function. Therefore, the general trend is that ASCs become less viable and functional with increasing BMI. This finding provides a new plan for obese patients who need plastic surgery, and patients who can reduce their BMI before surgery through exercise and diet control, or before bariatric surgery, and then undergo fat grafting surgery, and the ASCs vitality may be stronger than that of patients who do not undergo BMI lowering treatment.

Estrogen

Sex hormones have a significant effect on the growth and function of adipose tissue, and the concentration and activity of estrogen receptors in vivo are related to the biological function of ASCs, which is mainly manifested in the gradual increase of lipolytic activity, oxidative stress, and inflammatory response with the decrease of estrogen levels [52]. Geissler et al. [51] found that young women (premenopausal women < 45 years) who underwent fat grafting had higher survival rates compared with older women, suggesting a regulatory effect on estrogen levels. To further study the effect of estrogen on fat grafting outcomes, Zhou et al. [53] found that increasing the amount of estradiol in nude mice could improve the differentiation ability of ASCs, reduce apoptosis, and improve survival after transplantation. In addition, estradiol further improves the local microenvironment of lesions by enhancing the secretion of growth factors by ASCs, making it more conducive to tissue regeneration. One year later, Oruc et al. [54] obtained adipose tissue from groin pads from donor mice that underwent oophorectomy or sham surgery, and the fat grafts from "sham" mice were treated with softer grafts, more capillary density, and higher expression of pro-angiogenic factors due to their estrogen properties. Therefore, in the future, the appropriate addition of estradiol can be considered to improve the clinical effect when performing fat grafting, and the research in this field has broad prospects.

Donor site

There is still no consensus in the academic community on the effect of donor sites on the biological function of ASCs. Li et al. [55] reported that there were no statistically significant differences in the proliferation of ASCs derived from different donor sites. Xu et al. [56] found that the survival rate of ASCs in liposuction fluid was higher than that of the lateral thigh and abdomen. Cappellano et al. [57] showed that ASCs located in the superficial abdomen showed more pluripotency and stem cell characteristics than those located in the deeper layers. Current clinical data suggest that donor site selection has little effect on retention after fat grafting, and most clinicians choose donor locations based on safety, convenience, fat content, and patient preference. However, emerging evidence suggests that ASCs at different anatomical locations exhibit different morphological and functional differences, which may be co-regulated by cellular autonomy and developmental genes, such as higher concentrations of adrenergic receptors in abdominal adipose tissue than in buttocks, and in vitro studies of apoptosis induction have found that buttock ASCs show fewer signs of inflammatory damage than abdominal ASCs [58]. Therefore, it is recommended to use adipose tissue from the same donor site as much as possible in the treatment of nasolabial folds, cheeks, and other mirror areas, which can avoid different biological functions due to different sources of ASCs and minimize the difference in clinical effect.

Adipose tissue dysfunction is characterized by the loss of its homeostatic functions and is observed in obesity, insulin resistance, and diabetes. When physiological properties are disrupted in adipose tissue, increased production of cytokines and chemokines occurs with tissue infiltration by immune cells. In turn, immune cells also produce cytokines, metalloproteinases, reactive oxygen species, and chemokines that are involved in tissue remodeling, cell signaling, and immune regulation. The presence of inflammatory cells in adipose tissue affects its quality and today it is likely impossible to use it as a graft.

The effects of radiotherapy and chemotherapy

Currently, radiotherapy is increasingly used to treat human malignancies, with more than 50% of cancers requiring radiotherapy or palliative care. In addition to its beneficial anticancer effects, its late-onset complications are more unpredictable and progressively worsening. Early adverse effects of radiotherapy are due to the loss of functional cells due to cell death, but this does not explain the occurrence of late complications. Dörr [59] suggested that changes in human molecular signaling and the formation of reactive oxygen species after radiotherapy lead to single-stranded DNA breaks and preemptively activate senescent cells or accelerate terminal differentiation pathways. The above mechanism was further validated by animal experiments, and the results showed that the number of ASCs and the proliferative ability were significantly reduced after radiotherapy [60]. Given the time-dependent and dose-dependent effects of tamoxifen and alemtuzumab on ASCs, it may be beneficial to discontinue chemotherapeutic agents prior to fat grafting or to selectively cryopreserve adipose tissue prior to radiation therapy, so that ASCs have maximum biologic activity [61]. The other three commonly used chemotherapy drugs, cisplatin, camptothecin, and vincristine, did not show significant harmful effects, and whether to discontinue them before surgery can be determined based on the patient's condition [62].

Conclusions

The growing body of research underscores the critical role of donor-related factors, such as age, sex, BMI, donor site, and medical history, in determining the biological functionality of ASCs. The influence of estrogen in supporting ASC function has been particularly notable, highlighting the complex interplay between donor characteristics and cellular behavior. This review has consolidated the current understanding of how these donor factors impact ASC biology, providing valuable insights aimed at enhancing the clinical outcomes of fat grafting from the donor's perspective. Summarizing existing literature, this review has explored the nuanced effects of donor factors on ASC function. The insights gained offer crucial information for clinicians, enabling the creation of individualized treatment plans tailored to specific patient characteristics such as sex, age, weight, and underlying health status. Personalized approaches are pivotal in optimizing the effectiveness of fat grafting procedures and improving patient satisfaction.

Innovative strategies, such as adipose tissue cryopreservation, hold promise for mitigating the impact of donor factors on fat grafting outcomes [63]. The "bank of youth" concept, which involves extracting and cryopreserving adipose tissue from younger patients for future use, exemplifies a forward-thinking approach to preserve youthful cellular characteristics. Additionally, the development of acellular fat matrix transplantation presents a viable option for individuals with reduced ASC activity, potentially enabling allogeneic transplantation and in vivo adipogenic induction. Adipose tissue cryopreservation technology and the use of acellular fat matrices represent exciting avenues for future research. These advancements may address challenges associated with donor-related factors, ultimately improving the efficacy and predictability of fat grafting procedures [64–66]. As research progresses, the integration of these innovative techniques with a deeper understanding of donor variability will pave the way for more refined and successful fat grafting practices, enhancing both clinical outcomes and patient experiences. Further exploration into the mechanisms underlying donor-related variability is essential for advancing the field of fat grafting. Studies focusing on the molecular and genetic profiles of ASCs from diverse donor populations can provide a more comprehensive understanding of how intrinsic and extrinsic factors shape cellular function. Moreover, investigating the long-term outcomes of fat grafting in relation to specific donor characteristics will offer valuable insights into optimizing procedural protocols and improving graft retention rates. Clinicians and researchers must also consider the ethical and logistical challenges associated with innovative techniques like adipose tissue cryopreservation and acellular fat matrix transplantation. Establishing standardized guidelines and protocols for these procedures will be crucial in ensuring their safe and effective implementation in clinical settings. Additionally, fostering interdisciplinary collaboration among surgeons, cell biologists, and bioengineers will be key to translating these novel approaches from research to clinical practice.

In conclusion, understanding and addressing donor variability in ASCs is paramount for the advancement of autologous fat grafting. By integrating personalized treatment plans, leveraging innovative technologies, and continuing to investigate the underlying mechanisms of donor-related factors, the field can achieve more consistent and successful outcomes. This holistic approach will not only enhance the efficacy of fat grafting procedures but also significantly improve patient satisfaction and overall quality of life.

Abbreviations

ASCs: adipose (tissue)-derived stem cells

BMI: body mass index

BM-MSCs: bone marrow-derived mesenchymal stem cells

CLCs: cardiomyocyte-like cells

dASCs: diabetic adipose (tissue)-derived stem cells

IL-10: interleukin-10

S-ASCs: subcutaneous adipose (tissue)-derived stem cells

TGF-β1: transforming growth factor beta 1

VEGF: vascular endothelial growth factor

Declarations

Author contributions

OB: Conceptualization, Validation, Writing—original draft, Writing—review & editing, Funding acquisition. IG: Conceptualization, Methodology, Writing—original draft, Writing—review & editing. BZ and EM: Formal analysis, Investigation, Resources, Data curation. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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Consent to participate

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Consent to publication

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