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ORIGINAL ARTICLE BASIC SCIENCE/EXPERIMENTAL

Profile of Adipose-Derived Stem Cells in Obese and Lean Environments

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Abstract

Background With the demand for stem cells in regenerative medicine, new methods of isolating stem cells are highly sought. Adipose tissue is a readily available and non-controversial source of multipotent stem cells that carries a low risk for potential donors. However, elevated donor body mass index has been associated with an altered cellular microenvironment and thus has implications for stem cell efficacy in recipients. This review explored the literature on adipose-derived stem cells (ASCs) and the effect of donor obesity on cellular function.

Methods A review of published articles on obesity and ASCs was conducted with the PubMed database and the following search terms: obesity, overweight, adipose-derived stem cells and ASCs. Two investigators screened and reviewed the relevant abstracts.

Results There is agreement on reduced ASC function in response to obesity in terms of angiogenic differentiation, proliferation, migration, viability, and an altered and inflammatory transcriptome. Osteogenic differentiation and cell yield do not show reasonable agreement. Weight loss partially rescues some of the aforementioned features.

Conclusions Generally, obesity reduces ASC qualities and may have an effect on the therapeutic value of ASCs. Because weight loss and some biomolecules have been shown to rescue these qualities, further research should be conducted on methods to return obese-derived ASCs to baseline.

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Keywords Adipose-derived stem cell · Body mass index · Obesity · Fat graft · Lipotransfer · Fat graft retention

Introduction

The growing field of modern regenerative medicine requires the development of a reliable source of stem cells for tissue engineering and other medical applications.

Stem cells are characterized by the ability to self-regenerate and form multiple types of terminally differentiated cells. Embryonic stem cells are totipotent in their differentiation potential; adult stem cells are multipotent but with origins that are much less controversial. In fact, adipose tissue, which is commonly discarded after procedures such as liposuction, is an easily accessible and cost-effective source of adult stem cells. These adipose-derived stem cells (ASCs) can then be used in multiple therapeutic avenues, including healing of bone defects, organ repair, vascular regeneration and increasing the survival rate of fat tissue [1, 2].

The exploration of ASCs as a source of material in regenerative medicine has raised concerns about the

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optimal donor environment. Studies suggest that age, gender or anatomic location of harvest may affect ASC proliferation and differentiation potential [3–9]. For example, in one study ASCs from omental fat showed no difference in proliferation compared with ASCs taken from subcutaneous fat [7], while other studies suggest that subcutaneous ASCs may have greater capacity for proliferation, differentiation and survival compared with omental ASCs, possibly due to impairment of the AKT pathway [10].

Data on the role of obesity on ASC function are also mixed. Some studies suggest that body mass index (BMI) does not influence the concentration or yield of processed lipoaspirate cells [2, 11], while others report a positive [13, 14] or negative correlation [15]. The variable results could partially be explained by the error-prone, high subject variability and protocol-dependent nature of quantifying ASCs [16].

Because many ASCs are extracted from excess adipose tissue of donors who are overweight (BMI $>$ 25) or obese (BMI $>$ 30) ("obese ASCs"), the potential influence of this microenvironment has become clinically relevant. Healthy adipose tissue is increasingly seen not only as an energy reservoir but also as an endocrine organ with a role in normal metabolic regulation. However, adipocytes in obese patients have been shown to be dysfunctional because of their induction of a hypoxic and mildly inflammatory cellular microenvironment [17, 18].

The World Health Organization [19] estimated that more than 1 billion people worldwide are overweight (BMI $>$ 25), that 300 million are obese (BMI $>$ 30) and that the prevalence of obesity is increasing, with more than 20% of the US population already in the obese category. With a large proportion of the prospective donor ASCs in an environment produced by obesity, substantial efforts have been made to characterize that environment's effects.

The aim of the present study was to review the literature on ASCs and to elucidate the effect of donor obesity on cellular function.

Methods

A review of published articles on obesity and ASCs was conducted with the PubMed database and the following search terms: obesity, overweight, adipose-derived stem cells and ASCs. All studies published in English were included, including review articles, basic science and animal studies. Two investigators screened the titles, abstracts and full texts of the identified articles. The investigators extracted data related to specialty field, purpose of study, study design, intervention, results and conclusions. References of retrieved articles were scanned for additional studies. Data were collated using the narrative approach.

Results

The initial search strategy included a search of key terms including adipose-derived stem cell; body mass index; obesity; fat graft; fat graft retention. After eliminating the articles that were not relevant to the topic, selected articles were reviewed that specifically elucidated evidence for the effects of obesity on differentiation, proliferation, migration, viability, and an altered and inflammatory microenvironment. The results are summarized in Table 1.

Altered Environment

An important first step in understanding obesity's effects on ASCs is to characterize the obesity microenvironment. Obesity is one of the conditions, along with diabetes mellitus and aging, which induces cellular stress in the form of low-level inflammation and storage of excess lipids [17]. Generally, this is through adipocyte hypertrophy, coinciding with decreased angiogenesis and lipogenesis [20]. Interestingly, ASCs have been found to not only promote the generation of inflammatory macrophages but also to directly differentiate into those cells [21]. Therefore, the presence of inflammatory cells and cytokines in the adipose tissue of obese patients may be in large part due to site-specific mesenchymal ASCs [22, 23]. In addition, obesity increases the level of local and systemic circulating inflammatory cytokines and enhanced glucocorticoid production and thereby promotes migration of macrophages into the subcutaneous adipose tissue, adding another source to the inflammatory cells [24]. One of the upregulated cytokines potentially thought to increase this localization of inflammatory cells is osteopontin [25]. Nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) is heavily upregulated in obese ASCs in response to hypoxia, providing another mechanism for the increased inflammatory response [26].

Hypoxia has been noted in the white adipose tissue of obese mice, indicated by a 1.7-fold increase in lactate and an increase in bound pimonidazole, which forms adducts with thiol in hypoxic environments [18]. The hypoxia is due partly to a decrease in perfusion. Hypoxia-inducible factor 1 alpha subunit (HIF1A) is thought to be a key mediator in the hypoxia response by affecting cell survival and metabolism, and, as expected, it is decreased in obese ASCs [27].

Table 1 Summary of studies related to the effects of obesity on adipose-derived stem cells

References	Type	CEBM level of evidence	*n*	ASC origin	Main conclusion(s)
Bunnell et al. [1]	Methods review	5	–	–	Establishing viability of ASCs after isolation
Mojallal et al. [2]	In vitro	5	42	Lipoaspirate	No correlation between ASC yield and BMI; trend toward negative correlation of BMI and proliferation rate but not statistically significant
Van Harmelen et al. [7]	In vitro	5	29	Omentum and subcutaneous	Subcutaneous adipose tissue has a greater proliferation capacity than omental
Aksu et al. [8]	In vitro	5	6	Abdominoplasty	Male subcutaneous adipose tissue highest osteogenic differentiation potential versus female and omental
Geissler et al. [9]	In vitro	5	24	Lipoaspirate	No significant difference in ASC yield between obese and non-obese groups
Cleveland-Donovan et al. [10]	In vitro	5	15	Omentum and subcutaneous	Decreased replication of omental adipocytes versus subcutaneous
Faustini et al. [11]	In vitro	5	125	Lipoaspirate	BMI did not influence cell yield of ASCs
Yang et al. [12]	In vitro	5	66	Subcutaneous	BMI > 30 associated with enhanced adipogenic differentiation
Yu et al. [13]	In vitro	5	64	Lipoaspirate or abdominoplasty	Positive correlation between BMI and ASC yield; no significant difference in ASC proliferation in cohort analysis
Van Harmelen et al. [14]	In vitro	5	189	Reduction mammaplasty	Significant positive correlation between BMI and ASC count; significant decrease in differentiation capacity of ASCs with increasing BMI
Aust et al. [15]	In vitro	5	18	Lipoaspirate	Significant negative correlation between ASC yield and BMI
Bakker et al. [16]	In vitro	5	27	Omentum and subcutaneous	BMI not correlated to viable ASC number
Hosogai et al. [18]	In vitro	5	38	Subcutaneous	Adipose tissue of obese mice is hypoxic compared to non-obese
Baptista et al. [20]	In vitro	5	8	Abdominal subcutaneous	ASCs from formerly obese patients have poorer mitochondria function
Sailan-Barreau et al. [21]	In vitro	5		Abdominal subcutaneous and peri-renal adipose	Pre-adipocytes can engage in macrophage-like behavior in mice
Cousin et al. [22.]	In vitro	5		Adipose	ASCs isolated from obese mice produce inflammatory cytokines
Perez et al. [23]	In vitro	5		Bariatric adipose tissue	High levels of inflammatory markers in ASCs from obese environments do not affect their differentiation capacity
Lasselin et al. [24]	RCT; in vitro	2	37	Visceral adipose	Several inflammatory cytokines upregulated in obese peripheral adipose tissue
Nomiyama et al. [25]	In vitro	5		Adipose	Osteopontin mediates obesity-induced macrophage infiltration in mice
Petrangeli et al. [26]	In vitro	5	13	Subcutaneous and visceral	Upregulation of NfKB and inflammatory molecules in obese-derived ASCs
Perez et al. [27]	In vitro	10	5	Bariatric adipose tissue	Decreased proliferation and ASC yield in obese environments; changes in telomerase activity and telomere length resulting in decreased self-renewal capacity
Onate et al. [28]	In vitro	5	24	Subcutaneous	Reduced stemness and increased inflammatory markers; increased commitment to adipogenic differentiation

Table 1 continued

References	Type	CEBM level of evidence	*n*	ASC origin	Main conclusion(s)
Strong et al. [29]	RCT; in vitro	1b	12	lipoaspirate	Increased proinflammatory cytokines from human obese-derived ASCs, reducing therapeutic use in mouse MS model
Zhu et al. [30]	In vitro	5	14	Abdominal adipose	Obese-derived ASCs show osteogenic and adipogenic propensity
Lee et al. [31]	In vitro	5	39	Abdominal adipose	Inflammatory cytokines upregulated in ASCs derived from obese environments in Pima Indian pigs
Nair et al. [32]	In vitro	5	28	Abdominal adipose	Expression of inflammatory cytokines upregulated in ASCs from obese Pima Indian pigs
Roldan et al. [33]	In vitro	5	16	Omentum	Significant negative correlation between BMI and ASC proliferation; positive correlation between BMI and earlier ASC senescence
Orialo et al. [34]	In vitro	5			IL-6 promotes cell senescence via IL-1a
Strong et al. [35]	In vitro	5	12	Lipoaspirate	ASCs from obese environments have reduced osteogenic differentiation and collagen deposition
Onate et al. [36]	In vitro	5	8	Subcutaneous and lipoaspirate	Obesity decreased differentiation potential, angiogenic capacity and proliferation
Perez et al. [37]	In vitro	5	10	Subcutaneous	ASCs from obese environments show impaired migration and ASC differentiation capacity
Isakson et al. [38]	In vitro	5	51	Abdominal subcutaneous tissue	ASCs from obese environments have significantly impaired adipogenic differentiation potential
Wu et al. [39]	In vitro	5		Inguinal fat pad	CX3CR4 is crucial in ASC wound migration
Baek et al. [40]	In vitro	5		Lipoaspirate	Reproducible chemotaxis of ASCs via various growth factors
Frazier et al. [41]	In vitro	5	12	Cryopreserved lipoaspirate	Significant negative correlation between ASC proliferation and osteogenic differential potential in obesity
Moschen et al. [42]	Longitudinal	2	20	Subcutaneous and visceral	Significant decrease in inflammatory cytokines after weight loss
Viardot et al. [43]	Longitudinal	2	13	Subcutaneous and visceral	Significant decrease in inflammatory cell infiltration
Mitterberger et al. [44]	In vitro	5	12	Subcutaneous	Rapid weight loss increases ASC viability; obesity decreases cell viability and increases adipogenic differentiation
Baptista et al. [20]	in vitro	1b	8		Ex obese adipose tissue showed a higher number of small and large blood vessels
Perez et al. [45]	In vitro	5			Weight loss does not completely rescue ASC proliferation or viability
Silva et al. [47]	In vitro	5	25	Subcutaneous	Increased inflammatory cytokine secretion and IL-6 expression in obese; reduced adipogenic differentiation
Harris et al. [49]	In vitro	5	50	Lipoaspirate from elective vascular procedures	No significant correlation between ASC yield and BMI
Padoin et al. [50]	In vitro	5	25	Lipoaspirate	No significant correlation between ASC yield and BMI
Yoshimura et al. [51]	In vitro	5	–	Lipoaspirate	No significant correlation between ASC yield and BMI
Strong et al. [52]	In vitro	5	12	Lipoaspirate	Invasion gene upregulation
Carter et al. [53]	In vitro	5	2	Pre-adipocytes	Reduced gene expression of PPAR-γ and Adipo-Q; increased apoptotic resistance; reduced adipogenic differentiation in obesity

Table 1 continued

References	Type	CEBM level of evidence	*n*	ASC origin	Main conclusion(s)
De Girolamo et al. [48]	In vitro	5	15	Lipoaspirate	Reduced proliferation, clonogenic ability and adipogenic and osteogenic differentiation in obesity
Eljaafari et al. [54]	In vitro	5	6	Subcutaneous	Obese ASCs activate Th17 T cells and increase IL-17A secretion, PI3 K activation and inflammation
Oliva-Olivera et al. [55]	In vitro	5	47	Omentum	Obesity reduces osteogenic differentiation and proliferation and increases reactive oxygen species
Bullwinkle et al. [56]	In vitro	5	29	Lipoaspirate	Obesity increased leptin and IL-6 expression
Chehimi et al. [57]	In vitro	5	6	Subcutaneous mouse tissue	Obese ASCs activated IL-17A secretion; no difference in differentiation
Ejaz et al. [58]	In vitro	5	21	Subcutaneous	Obesity increased IGF-1, reduced autophagy and increased adipogenesis
Pachon-Pera et al. [59]	In vitro	5	21	Lipoaspirate	Obesity increased migration and invasion and decreased adipogenic differentiation
Patel et al. [60]	In vitro	5	2	Omental	Obesity altered stem cell markers and senescence
Serena et al. [61]	In vitro	5	12	Visceral	Obesity increased inflammation, metabolic activity, migration, phagocytosis and invasion
Mariani et al. [62]	In vitro	5	12	Visceral and subcutaneous	Sirtuin1-6 mRNA in obesity ASCs were increased in subcutaneous tissue and decreased in visceral tissue
Mastrangelo et al. [63]	In vitro	5	5	Lipoaspirate	Obesity increased glycolysis, TCA and pentose phosphate pathways
Togliatto et al. [64]	In vitro	5	16	Visceral and subcutaneous	Obesity reduces angiogenic potential and VEGF, MMP-2 and ERK1/2
Zhang et al. [65]	In vitro	5	39	SVF	Obesity increased ASC circulation, cytokine expression and tumor homing in prostate cancer
Marcelin et al. [66]	In vitro	5	34	Adipose	Platelet-derived growth factor reception (PDGFR) develop a myofibroblastic phenotype
Oliva-Olivera et al. [67]	In vitro	5	60	Visceral and subcutaneous	Obesity decreases adipogenesis and clonogenic potential
Perez et al. [68]	In vitro	5	10	Subcutaneous	Obesity decreases adipogenic differentiation
Oliva-Olivera et al. [69]	In vitro	5	35	Omentum	Obesity increases inflammatory cytokines under hypoxia
Gesta et al. [70]	In vitro	5	198	Subcutaneous and visceral	Genome-wide expression profiles show no difference between subcutaneous and visceral cells
Tchkonia et al. [71]	In vitro	5	12	Subcutaneous and visceral	Proliferation and adipogenic potential greater in subcutaneous compared to visceral
Tchkonia et al. [72]	In vitro	5	31	Subcutaneous and visceral	Adipogenic potential and resistance to apoptosis greater in subcutaneous compared to visceral
Tchkonia et al. [73]	In vitro	5	18	Subcutaneous and visceral	Adipogenic potential and resistance to apoptosis greater in subcutaneous compared tovisceral
Tchkonia et al. [74]	In vitro	5	16	Subcutaneous and visceral	Adipogenic potential in subcutaneous greater than visceral
Perrini et al. [75]	In vitro	5	15	Subcutaneous and visceral	MCP-1, IL-6, GM-CSF and VEGF secretion greater in visceral compared to subcutaneous
Fernández et al. [76]	In vitro	5	8	Subcutaneous and pre-peritoneal	Proliferation greater in subcutaneous; adipogenic potential greater in pre-peritoneal
Hauner et al. [77]	In vitro	5	14	Subcutaneous and visceral	Adipogenic potential greater in subcutaneous compared to visceral
Shahparaki et al. [78]	In vitro	5	18	Subcutaneous and visceral	Adipogenic potential greater in subcutaneous compared to visceral
Macotela et al. [79]	In vitro	5	-	Subcutaneous and visceral	Proliferation and adipogenic potential greater in subcutaneous compared to visceral

Table 1 continued

References	Type	CEBM level of evidence	*n*	ASC origin	Main conclusion(s)
Digby et al. [80]	In vitro	5	-	Subcutaneous and visceral	Adipogenic potential greater in subcutaneous compared to visceral
Niesler et al. [81]	In vitro	5	12	Subcutaneous and visceral	Adipogenic potential greater compared to visceral

In general, there is reduced ASC function in response to obesity in terms of angiogenic differentiation, proliferation, migration, viability, and an altered and inflammatory transcriptome. Osteogenic differentiation and cell yield do not show reasonable agreement. Weight loss partially rescues some of the aforementioned features

ASCs adipose-derived stem cells, *BMI* body mass index, *IL* interleukin, *RCT* randomized controlled trial, *NfKB* nuclear factor kappa-light-chain-enhancer of activated B cells, *mRNA* messenger RNA, *SVF* stromal vascular fraction

One study [20] showed that even after bariatric surgery-induced weight loss, the ASCs isolated from a formerly obese patient's adipose tissue still showed negative effects on mitochondrial function. These ASCs also remained more proadipogenic despite the patient having a normal BMI, potentially through epigenetic mechanisms, which may explain why many obese patients have difficulty maintaining weight loss.

Altered Transcriptome Profile

Superficially, many surface markers on obese ASCs are similar to those on ASCs from lean donors (e.g., CD29, CD44, CD90 and CD105) [28]. On further investigation, obesity-induced inflammation can cause lasting functional differences in ASCs from obese donors. One study [29] showed increased mRNA expression of proinflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin (IL)-6 by obese ASCs, which further caused no clinical improvement when used in murine models of multiple sclerosis. Additionally, a study [26] showed strong upregulation of NFkB in response to hypoxia.

These results were bolstered by a study [30] of domestic pigs fed an atherogenic diet compared with pigs fed normally for 16 weeks. At the end of the study, ASCs in the obese pigs expressed higher amounts of TNF-α, which further correlated in vitro with enhanced adipogenic and osteogenic differentiation. Lee et al. [31] also found overexpression of the chemokines monocyte chemotactic protein 1 (MCP1) and macrophage inflammatory protein 1 (MIP1) and overexpression of fibronectin adhesion molecules, which, respectively, attract macrophages to tissue and retain them. Further, Nair et al. [32] showed an upregulation of various inflammatory genes, including IL-8 and CD53 in ASCs isolated from obese Pima Indians. Several microRNAs implicated in differentiation and cell senescence are upregulated in obese ASCs [33]. Another cause of cell senescence is high levels of IL-6 and IL-8 [34]. Thus, the preponderance of evidence points to ASCs not only being influenced by but contributing to the low-grade inflammatory environment in obesity.

Differentiation Potential

ASCs, as multipotent cells, have the potential to revolutionize reconstructive surgery by increasing the availability of high-demand tissue types. For example, the reconstruction of craniomaxillofacial defects, whether inherited or acquired, is often limited by the scarcity of available bone tissue. In one study [35], ASCs from lean persons showed an increased propensity toward osteogenic differentiation compared with ASCs from obese persons, both in vitro and in vivo. When the obese ASCs were supplemented with estradiol, they regained their osteogenic propensity. Likewise, the osteogenic potential of omental ASCs from subjects with different metabolic profiles was assessed by Oliva-Oliveira et al. [55] and found that the ASCs from subjects without metabolic syndrome have a greater osteogenic, clonogenic, fibrotic potential and proliferation rate than those from subjects with metabolic syndrome. These studies contradict the previously mentioned study by Zhu et al. [30] that used porcine models of obesity and found increased osteogenic differentiation in obese ASCs that correlated with increased TNF-α expression. The finding also contradicts the study by Yang et al. [12], which showed an increase in osteogenic differentiation potency with increasing BMI in human ASCs.

Obese ASCs also showed reduced overall differentiation and angiogenic differentiation potential compared with ASCs from lean donors, limiting their efficacy as regenerative tools [14, 36, 37]. Roldan et al. [33] showed that this reduction in differentiation capacity was associated with dysregulation of Sonic Hedgehog, Wnt and Notch signaling pathways. Isakson et al. [38] also showed that dysregulation of Wnt and increased TNF-α led to a proinflammatory, macrophage-like phenotype that limited

the normal differentiation capacity of ASCs. Obese ASCs also exhibit decreased expression of genes essential to embryogenesis, wound repair and angiogenesis such as the HOX [28]. Additionally, Harris et al. [49] assessed the availability of ASCs in old patients with comorbidities (obesity, diabetes, renal or peripheral vascular disease) that underwent vascular surgical procedures. They demonstrated that ASCs can acquire endothelial specific trials in these patients, and that adipose tissue is a practical source of autologous, adult stem cells for vascular tissue engineering.

Migration Potential

To effectively aid wound healing and other regenerative processes, ASCs must be able to migrate to injured tissue with the aid of chemotactic factors such as stromal-derived factor 1 (SDF1), the CXC chemokine ligand 16 (CXCL16) and the CXC chemokine receptor 4 (CXCR4) [39]. Reliably reproducible chemotaxis would potentially even allow the intravenous delivery of ASCs to distant injury sites within the body [40]. Onate et al. [28] showed that obese ASCs had significantly lower expression of SDF1 compared with ASCs from lean controls, indicating that obesity may affect the delivery of ASCs to injured tissue. In contrast, another study [37] showed that when responding to stimuli such as MCP1 and high-mobility group box 1 protein (HMGB1), obese ASCs doubled their migration capacity; however, under basal conditions that population had a reduced migration capacity because there is no dose-dependent response in migration to chemotactic factors such as TNF-α, SDF1 or IL-8.

ASCs from obese adipose tissue showed an altered pattern of cell surface marker expression with differences in proliferation, migration and differentiation capacity in both undifferentiated and differentiated stages [59]. This change in plasticity observed in obese-derived ASCs is maintained in the absence of hypoxia, suggesting that these cells might be obesity conditioned. Additionally, adipose-derived stem cells of obese and lean individuals showed differences in their cell markers, exosome contents and percentage of senescence cells [60].

Proliferation Potential

The preponderance of studies shows that obese ASCs have impaired proliferation potential and decreased cell survival [26, 27, 41]. One study [2], however, found no significant correlation between BMI and proliferation. Pérez et al. [27] found a significantly increased population doubling time in ASCs from obese mice and humans compared with ASCs from lean mice and humans. The study also found an increased fraction of pre-apoptotic cells in obese ASC populations. This could potentially be due to the reduced telomerase activity and upregulation of p21, increasing DNA instability and apoptosis, respectively [27]. Mariani et al. [62] evaluated the expression of sirtuins (modulators of adipose tissue metabolism) in adipose-derived stem cells from subcutaneous and visceral fat of obese and lean subjects. They found that sirtuins' expression in visceral stem cells correlated negatively with body mass index and C-reactive protein, and positively with peroxisome proliferator-activated receptor (PPAR) delta, which is consistent with a protective effect against visceral obesity and inflammation.

Obese persons do not all have the same microenvironment in their tissues, but the presence of metabolic syndrome is indicative of a certain subset of cells. Onate et al. [36] reported that only ASCs from patients with metabolic syndrome had a significantly higher population doubling time than ASCs from normal weight or metabolically healthy obese patients. Another study by the same group [28] was able to differentiate increasing degrees of impairment between healthy lean persons, healthy obese persons and obese persons with metabolic syndrome. In addition, the consequences of this proinflammatory status with insulin resistance and type 2 diabetes were studied by Eljaafari et al. [54]. They cocultured ASCs from obese individuals with mononuclear cells and demonstrated inhibition of adipocyte differentiation mRNA markers and impaired insulin-mediated Akt phosphorylation and lipolysis inhibition through an ASC-Th17-monocyte cell axis. This novel proinflammatory process, in turn, inhibits adipogenesis and adipocyte response to insulin [54, 57]. These data support the theory that the donor metabolic phenotype compromises the immunomodulatory properties of ASCs [61]. Metabolic derangement also limits the life span of ASCs from obese persons; in a porcine model of obesity, ASCs showed increased senescence compared with ASCs from lean pigs [30].

Weight Loss

As mentioned previously, ASCs isolated from previously obese persons have been reported to be proadipogenic and maintain negative mitochondrial function. Thus, because previously obese persons may be an important source of ASCs, it is important to characterize ASCs isolated from this environment. Some studies have shown a significant decrease in inflammatory cytokines [42] and inflammatory cell infiltration [43] in subcutaneous adipose tissue after weight loss. However, effects on ASCs themselves have been less encouraging. Mitterberger et al. [44] found no change in ASCs isolated from previously obese patients. Indeed, ASCs from the previously obese group achieved an adipocytic phenotype faster than those isolated from lean

patients [44, 45]. However, Petrangeli et al. [26] noted that obese ASCs recovered differentiation potential features after hypoxia, and Perez et al. [46] noted that ASCs from formerly obese mice partially recovered viability. A study [45] also showed that ASCs from previously obese patients had the same osteogenic potential as those from controls. Silva et al. [46] found that formerly obese ASCs showed partial recoveries to non-obese baseline in proliferation, cell morphology and migration potential but not live cell fraction or angiogenic potential. Furthermore, Ejaz et al. [58] identified DIRAS3 and IGF-1 as long-term target genes upregulated in ASCs in adipose tissue of donors with weight loss. DIRAS3 down-regulates Akt-mTOR signaling and thus inhibits adipogenesis and activates autophagy in ASCs of formerly obese patients. More generally, in a study examining the effects of bariatric surgery in women, ASCs from previously obese patients showed the most lipid accumulation and secreted more MCP1, an inflammatory cytokine [47]. The data suggest that although inflammation is generally reduced after weight loss, ASC differentiation potential and transcriptome profile do not completely return to baseline.

Discussion

Obesity has been associated with a chronic inflammatory state and altered cellular microenvironment and thus has implications for stem cell efficacy in recipients. Furthermore, it is linked to endocrine and metabolic dysfunction, insulin resistance and oxidative stress. The complex mechanisms by which obesity impacts adipose tissue physiology are outside of the scope of this article; however, elucidating the impact on adipose-derived mesenchymal stem cells is our primary objective.

ASCs have multiple functions including cell renewal, spontaneous repair and homeostasis. ASCs are prominent tools in regenerative medicine due to their abundance, ease of isolation and multipotent capacity. Due to the dynamic use of fat grafting across clinical applications, much effort has been taken to understand the impact of patient characteristics on fat graft viability. This review synthesizes data to support that ASCs derived from obese donors exhibit compromised properties, affecting many properties including differentiation, proliferation, metabolism and immunomodulation.

Despite significant progress in stem cell research, adipogenesis is a highly complex process and the mechanisms governing inter-related pathways remain ill-defined. Nonetheless, metabolic health seems to have a larger role than a strict BMI cutoff in predicting the performance of ASCs. The presence of metabolic derangement due to obesity results in an inflammatory cellular microenvironment, which reduces the proliferation potential of ASC and reduces the ASC pool [48, 49]. In terms of angiogenic differentiation potential, obesity appears to have a negative role; for osteogenic potential, the relation is less clear. This may be an important distinction for ASCs used in scaffolds and other bone grafts. Additionally, studies show that obesity may decrease the therapeutic value of ASCs by altering the cell transcriptome, impairing migration, slowing doubling time and hastening senescence.

Most of the evidence presented in this review is from in vitro studies, which may not correspond to what occurs in vivo. Many of the studies rely heavily on animal models of diet-based obesity for a set amount of weeks. Further research should attempt to model human obesity more accurately, while accounting for stress level, genetics and amount of exercise. This would more accurately predict the effect of donor obesity on ASCs and thus, the efficacy of using these cells in regenerative medicine.

Future research should also elucidate methods by which obese-derived ASCs may be returned to their healthy state, which some studies have found with estradiol, TNF-α and weight loss. According to the current body of knowledge, the assumption can be made that ASCs derived from obese, metabolically unhealthy donors do not have the same properties and are potentially less therapeutically valuable compared with those derived from lean, healthy donors. This should be taken into account when ASCs are used for clinical purposes.

Conclusions

Adipose tissue is a readily available source of multipotent stem cells that carries a low risk for potential donors. This review synthesizes the evidence for donor obesity on adipose-derived stem cell function. Obesity has been associated with a chronic inflammatory state and altered cellular microenvironment and thus has implications for stem cell efficacy in recipients. The compromised ability of ASCs to proliferate in obese subjects should be considered in applications of cell-based technologies and therapies such as tissue engineering, stem cell banking and fat grafting. In general, obesity affects angiogenic differentiation, proliferation, migration, viability and alters the inflammatory transcriptome. Because weight loss and some biomolecules have been shown to rescue these qualities, further research should be conducted on methods to return obese-derived ASCs to baseline.

Authors' Contributions KSV, HCV, SM, KB were involved in conception or design of the work. KSV, HCV, SM, KB, MB, JMB,

JM-J, NT, VL contributed to data collection, analysis and interpretation. KSV, HCV, SM, KB, MB, JMB, JM-J, NT, VL were involved in drafting the work or revising it critically for important intellectual content.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest to disclose.

Statement of Human and Animal Rights or Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent For this type of study, informed consent is not required.

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