Chapter

Subcutaneous Adipose Stem Cells in Obesity: The Impact of Bariatric Surgery

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Abstract

Adipocyte expansion, which involves adipose tissue-derived mesenchymal stem cells (ASCs), is a critical process with implications in the pathogenesis of metabolic syndrome and insulin resistance associated with obesity. Impaired subcutaneous adipogenesis leads to dysfunctional, hypertrophic adipocytes, chronic low-grade inflammation, and peripheric insulin resistance. Alternatively, it has also been proposed that the preservation of the functionality of subcutaneous adipocyte precursors could contribute to some obese individuals remaining metabolically healthy. Very few studies evaluated the changes in the adipogenic differentiation for human subcutaneous ASCs following bariatric surgery. Weight loss after bariatric surgery involves extensive remodeling of adipose tissue, comprising the hyperplasia-hypertrophy balance. Subcutaneous ASCs may be implicated in the variations of bariatric outcomes, through a different restoration in their proliferative and adipogenic potential. Weight loss induced by bariatric surgery correlates to the subcutaneous ASC functions and could explain the variability of metabolic improvement. Limited research data are available to the present and these data support the importance of diagnosis of subcutaneous ASCs functions as predictors of metabolic improvement after bariatric surgery.

Keywords: obesity, bariatric surgery, adipose tissue, adipose-derived stem cells

1. Introduction

Excess fat accumulation in adipose tissue causes obesity, which increases the risks of metabolic syndrome, diabetes, cardiovascular disease, and cancer. White adipose tissue (WAT) includes subcutaneous and visceral adipose tissue (SAT and VAT) with different metabolic features. SAT protects from metabolic disorders, while VAT promotes them [1].

SAT is the most important adipose tissue deposit and is characterized by its capacity to expand in reponse to surplus of energy. However, in the context of obesity, when the storage capacity of SAT is exceeded, fat is stored in other undesirable sites such as visceral depot or non-adipose organs (liver, skeletal muscle, myocardium, and pancreas). Impaired adipocyte development is associated with insulin resistance, so hypertrophic SAT is an important link with obesity-induced metabolic dysfunctions [2].

Adipocytes come from mesenchymal stem cells in the stroma of adipose tissue. These mesenchymal stem cells become preadipocytes when they lose their ability to differentiate into other mesenchymal lines and intervene in the adipocyte line. The second phase of adipogenesis is terminal differentiation, through which preadipocytes acquire the characteristics of mature adipocytes, acquiring lipid droplets and the ability to respond to hormones such as insulin. Terminal differentiation consists of a cascade of transcriptional events [3].

The number of mature adipocytes present in adipose tissue is largely determined by the ability of the limited number of preadipocytes to undergo the process of differentiation and the availability of mesenchymal cells to be differentiated into new preadipocytes when necessary [3]. Because new adipocytes are considered protective against metabolic dysfunction, it is plausible that the maladaptive adipogenesis could be involved in the pathogenesis of metabolic syndrome and insulin resistance associated with obesity [4]. In vitro studies have confirmed a decrease in the ability of adipogenic differentiation of ASCs in obese people.

The individual "set point" and the ability to expand the SAT depends on both the individual's genetic background and lifestyle. Studies have shown that obese people, metabolically healthy, have preservation of the architecture and functionality of adipose tissue. Women can recruit new fat cells in the femural or gluteal region at maturity. This ability to expand lower-body fat may reduce the abdominal subcutaneous adipocyte hypertrophy and the accumulation of ectopic visceral fat in obese women. By contrast, the reduced ability to expand SAT in lower-body region is observed in men and this is accompanied by the accumulation of fat in subcutaneous abdominal and visceral adipose tissues [5].

Adipocyte expansion, which involves adipose tissue-derived mesenchymal stem cells (ASCs), is a critical process with implications in the pathogenesis of metabolic syndrome and insulin resistance associated with obesity. Impaired subcutaneous adipogenesis leads to dysfunctional, hypertrophic adipocytes, chronic low-grade inflammation, and peripheric insulin resistance. Alternatively, it has also been proposed that the preservation of the functionality of subcutaneous adipocyte precursors could contribute to some obese individuals remaining metabolically healthy. Very few studies evaluated the changes in the adipogenic differentiation for human subcutaneous ASCs following bariatric surgery. Weight loss after bariatric surgery involves extensive adipose tissue remodeling, implicating mechanisms underlying adipose tissue plasticity, and the adipogenic potential.

2. Subcutaneous adipose stem cells

Isolation of subcutaneous human adipose stem cells

SAT consists predominantly of adipocytes, but also contains other cell populations generally referred to as the stromal vascular fraction (SVF). Studies from the 1970s first revealed that fibroblast-like cells from the cultures of the SVF [stromal vascular cultures (SVCs)] could be propagated and differentiated into mature adipocytes in vitro. These in vitro stromal vascular-derived adipocytes, named adipose stem cells (ASCs), molecularly resemble the adipocytes found in their depot of origin [6]. After the isolation and proliferation of these ASCs, they can be used for the experimental study of the molecular processes in regulating adipocyte differentiation [7].

SAT can be isolated by a minimally invasive liposuction procedure. Tissue separation studies have involved the adipose stromal and vascular compartment as the site of origin of adipose stem cells. The SVF is operationally defined as a

heterogeneous mixture of cells, isolated by enzymatic dissociation and density-based separation, a procedure designed to remove the group of cells that were in the deposits around the floating adipocytes. These stromal-vascular cells represent a rich potential resource for examining a variety of ambiguities relevant to adipogenesis as well as regenerative medicine [8].

Identification of human subcutaneous adipose stem cells

Multiple cell-surface makers were demonstrated for ASC identification. The ASC immunophenotype should display the following typical marker profile for stromal cells: CD44, CD73, CD13, CD90, CD29 positive, and CD34 positive, but CD31, and CD45 negative [9]. Subcutaneous-ASC markers included CD10 and CD141 as potential cell-surface makers [10].

Compared with visceral-ASCs, subcutaneous-ASCs expressed a high level of CD90 and showed increases in proliferation, mitotic clonal expansion, and adipogenic differentiation. CD90 silencing inhibited proliferation and mitotic clonal expansion of subcutaneous-ASCs [1].

Adipogenic differentiation

Adipogenesis is the process of cell differentiation from stem cells to adipocytes. During this process, the ASCs will divide into two cells, where one cell keeps the stemness and the other cell can commit to the adipogenic lineage and become preadipocyte. The preadipocytes are fibroblast-like cells that are morphologically indistinguishable from the mesenchymal precursors but they lose their capacity to differentiate into other cell types (osteocytes, chondrocytes, myocytes, etc. The preadipocyte can terminal differentiate and acquire the characteristics of mature adipocytes, including lipid synthesis, insulin sensitivity, and the secretion of adipocyte-specific proteins. The terminally-differentiated adipocytes are characterized by a large unilocular lipid droplet and their main function is energy storage [11].

Adipogenesis is a well-orchestrated process that requires sequential activation of numerous transcription factors, including the CCAAT gene family/enhancer-binding protector (C/EBP) and peroxisomal proliferator-activated receptor-γ (PPAR-γ) [12]. The molecular mechanisms of adipogenesis involve stimulators and inhibitors. Adipogenic stimulators are represented by peroxisome proliferator-activated γ receptor (PPAR γ), insulin-like growth factor I (IGF-1), macrophage colony-stimulating factor, fatty acids, prostaglandins, and glucocorticoids. The inhibitors are Wnt, transforming growth factor-β (TGF-β), inflammatory cytokines, and growth hormone. Adipogenesis could be also influenced by age, gender, adipose depot, and lifestyle [13].

In vitro studies showed that mRNA expression level of CD10 of subcutaneous-ASCs increased after adipogenic stimuli, and this increase positively correlated with those of adipogenic markers, PPARG and aP2. In contrast, the CD200 level decreased after adipogenesis was initiated and exhibited a negative correlation with adipogenic markers [10].

Microenvironment of ASCs

Stem cells are found in a specialized environment, a niche, which controls many aspects of cell behavior - activity, proliferation, and differentiation The microenvironment of the subcutaneous stem cell (niche) refers to a specific location în which the adult subcutaneous cells reside and interact with ASCs and other cells or substrates. The surrounding microenvironment of ASCs provides signals that keep ASCs quiescent or promote either proliferation or differentiation. However, the niche function is to prevent ASC proliferation or differentiation. Several important factors regulate ASCs' characteristics within the niche, including cell–cell and cell-extracellular matrix (ECM) relationships, growth factors, oxygen tension, and cytokine signals [11].

3. Subcutaneous ASCs differentiation in obesity

In obese patients, adipose tissue expands by differentiating preadipocytes into adipocytes (adipogenesis) and/or hypertrophy of existing adipocytes. Adipocytes hyperplasia is the alternative optimal process for sustaining the high demand for lipid storage, through the activation of multipotent stem cells, leading to the generation of new mature adipose cells, but it has a limited and individualized capacity [14, 15].

The low adipogenic capacity of subcutaneous ASCs may result in a dysfunctional tissue, because it leads to adipocyte hypertrophy, causing the accumulation of inflammatory macrophages; insulin resistance; and also the accumulation of ectopic fats in the liver, muscles, kidneys, and pancreas [16–21].

The subcutaneous ASC functions are altered in obese patients. The literature review on the relationship between obesity and adipogenic differentiation capacity of mesenchymal stem cells originating in subcutaneous adipose tissue obtained from pre-surgical obese patients are shown in **Table 1**.

Several studies found that lipid accumulation in hypertrophic subcutaneous adipocytes evaluates the expansion capacity of the pre-adipogenic mesenchymal cell line and lipid overloaded adipocytes are associated with a poor metabolic profile for obese patients [28–30]. The subcutaneous adipose tissue represents 90% of total fat mass, it has the potential to greatly affect systemic insulin resistance via adipokine secretion in obese persons [31].

The obese population is known to be at high risk for cardio-metabolic diseases. Insulin resistance evaluation by HOMA-IR is considered as a good cardiovascular

Study (authors, year)	Results regarding adipogenesis	Particularities (group/study)
De Girolamo et al., 2013 [22]	Reduced ASCs proliferation and slightly reduced differentiation in obese vs. non-obese patients;	Human subcutaneous ASCs from bariatric obese patients (BMI > 35 kg/m^2, N = 8) vs. non-obese (BMI < 30 kg/m^2, N = 7);
Frazier et al., 2013 [23]	Reduced ASCs proliferation in overweight patients, without significant effect on adipogenic differentiation;	Human lipo-aspirate isolated ASCs overweight patients (BMI > 25 kg/m^2, N = 6) vs. normal weight patients (BMI < 25 kg/m^2, N = 8);
Hristov et al., 2019 [24]	Reduced adipogenic potential. Negative correlations with HOMA-IR and leptin/ adiponectin ratio.	Human subcutaneous ASCs from bariatric obese women (N = 20; BMI = 45 ± 10 kg/m^2) and normal weight women (N = 7; BMI = 24.5 ± 2.5 kg/m^2);
Muir et al., 2016 [25]	No difference in preadipocyte frequency between DM and NDM subjects was observed in SAT.	Human subcutaneous ASCs from bariatric obese patients: diabetic, DM (BMI =47 kg/m^2; N = 34) and non-diabetic, NDM (BMI =47 kg/m^2; N = 48)
Oliva-Olivera et al., 2017 [26]	Reduced adipogenic gene expression in overweight patients;	Human subcutaneous ASCs; overweight patients (BMI > 25 kg/m^2, N = 20) vs. normal weight patients (BMI < 25 kg/m^2, N = 40);
Pachón-Peña et al., 2016 [27]	Reduced proliferation and migration capacity, and reduced adipogenic differentiation potential independent of oxygen tension;	Human lipo-aspirate isolated ASCs from obese patients (N = 8; BMI: 35 ± kg/m^2) and normal weight patients (N = 8; BMI = 23 ± 1 kg/m^2);

Table 1.
Relationship between subcutaneous ASCs and obesity in pre-surgical patients.

risk predictor [32], is also demonstrated as a valuable criterion for identifying obese individuals with a higher mortality risk by Hinnouho et al. [33].

Insulin resistance and its cardio-metabolic consequences are closely associated with disturbances of fat metabolism, as it was demonstrated that exceeding the subcutaneous adipose tissues storage capacity results in fatty acid infiltration of insulin target tissues like the skeletal muscle and the liver [34], a phenomenon known as lipotoxicity that is intimately related to the development of insulin resistance.

The estimated prevalence of obese patients without metabolic syndrome criteria in a recent meta-analysis is 35% of the obese patients [35], so it becomes important to better understand the particularities of adiposity expansion in these obese patients that do not develop insulin-resistance or associated metabolic disturbances.

Effects of hyperglycemia and oxidative stress on subcutaneous ASC adipogenesis

Diabetes impairs the angiogenic potential of adipose-derived stem cells by selectively depleting cellular subpopulations. Studying adipogenic potential of adipose tissue-derived from diabetic type 1 or type 2 mice, Rennert et al. [36] observed depletion of putative ASCs (CD45-/CD31-/CD34+ cells) within the diabetic SVF, which was consistent with the signaling dysfunction seen in this environment.

Recent studies have shown the widespread downregulation of mesenchymal stem cell markers in the SAT of diabetic rats. ASCs derived from obese mice [37] and Zucker diabetic fatty rats [38] exhibited a reduced capability for adipogenic differentiation associated with a decreased expression of related genes insulin receptor substrate 1 (IRS1), insulin receptor substrate 2 (IRS2), and adipocyte fatty acid-binding protein (aP2 or FABP4) compared with mouse control ASCs.

The oxidative stress generated by hyperglycemia has deleterious effects on proliferation, survival, homing, and angiogenic capacity of ASCs derived from the stromal vascular fraction [11, 39, 40]. Hyperglycemia up-regulates reactive oxygen species (ROS) production, suppresses the nitric oxide (NO) synthesis pathway, thereby may impair the regenerative function of ASCs. Impaired adipogenesis and IR were associated with increased 4-HNE, increased 8-hydroxy-2-deoxyguanosine (8-OHdG), increased cholesterol oxidation-derived oxysterols [41]. Also, it was demonstrated that the heme oxygenase-1 inhibited proliferation and differentiation of preadipocytes at the onset of obesity via reactive oxygen species-dependent activation of Akt/PKB (protein kinase B) in obese mouse models [42].

The mechanism of decreased number of stem cells in murine diabetic adipose tissue may involve the activation of hyaluronan synthases in intracellular membrane compartments [43]. The study by Han et al. [44] showed that extended extracellular hyaluronan matrices were found around adipocytes in obese mice. The matrix was infiltrated with macrophages, which would otherwise accumulate because adipocytes would continue to synthesize and extrude hyaluronan indefinitely in response to sustained hyperglycemia. The stem cells that divide into hyperglycemia (> 2.5 times normal) are heading for pathological adipogenesis in response to glucose stress and that subsequent cell divisions along this pathway could contribute to the expanded population of fat cells in adipose tissue in diabetes.

Effects of pro-inflammatory signals on subcutaneous ASC adipogenesis

Obesity is characterized by the accumulation of diverse immune cells in both the subcutaneous and visceral expanding fat depots, even though macrophage infiltration appears to be more prominent in the latter [45]. The presence of macrophages in the human SAT is causally related to impaired ASCs differentiation, which in turn is associated with systemic IR. A negative correlation between SAT adipogenesis, but not VAT, and systemic IR was observed [46]. Moreover, lipid-laden adipocytes produce increased levels of cytokines such as Interleukin 6 (IL-6), IL-1β, IL-8, TNF-α, and monocyte chemoattractant protein-1 (MCP-1), which can inhibit preadipocyte differentiation [41].

To investigate the inflammatory state in diabetes, the levels of IL1β, IL-6, and TNFα were measured. Numerous studies have shown these cytokines reduce adipogenesis. In patients with diabetes, IL-1β has been shown to induce insulin resistance (IR) in adipocytes by reducing IRS-1 regulation. Also, decreased IRS-1 expression has been reported to inhibit adipogenesis by decreasing CEBPα and PPARγ. Finally, the expression of SIRT1 is downregulated compared to that of healthy cells, this finding is consistent with other studies showing that inhibition of this enzyme increases senescence and reduces the proliferation of MSCs, losing their adipogenic potential [21].

Recent studies revealed that IL-6 may be a good marker of subcutaneous adipose tissue inflammation and it is inversely related to adipogenic capacity. Subcutaneous ASCs derived from insulin-resistance obese individuals exhibited a lower pro-adipogenic and higher anti-adipogenic gene expression profile This diminished adipogenic potential of ASCs may be a consequence of a preponderance of large adipocytes, prone to forming inflammatory foci. Markers of oxidative stress were also elevated in the IR state. Thus the related scenario of inflammation and oxidative stress is a likely mediator of increased IL-6 secretion in this depot [47].

4. Bariatric surgery impact on subcutaneous ASCs differentiation

Bariatric surgery is widely acknowledged as the most effective treatment for obesity (Frikke-Schmidt, O'Rourke et al. 2016). The most obvious effect of bariatric surgery is a loss of up to half of the total adipose tissue mass within the first year after surgery along with improvements in systemic metabolism.

Weight loss after bariatric surgery involves extensive remodeling of adipose tissue, comprising the hyperplasia-hypertrophy balance. The bariatric intervention has variable results, with up to 35% of patients achieving suboptimal weight loss [48]. ASC adipogenic potential correlates of metabolic disease and therapeutic responses are poorly defined. Very few published data that correlate changes in weight loss induced by bariatric surgery and preadipocyte functions (**Table 2**).

In obesity, subcutaneous ASCs have abnormal functions in terms of angiogenic differentiation, proliferation, migration, viability, and an altered and inflammatory transcriptome [51, 52]. Weight loss partially rescues some of the aforementioned features.

An important improvement in glycemia is seen in obese patients with diabetes who undergo bariatric surgery, even before clinically significant weight loss occurs. A decrease of 50% in HOMA-IR is seen within 1 week following surgery [53]. Partial or total remission rates in type 2 diabetes as high as 80–90% have been observed to occur following bariatric surgery [54, 55].

Few studies have successfully measured local inflammation within subcutaneous adipose tissues after surgery in human studies. However, these limited findings do indicate that adipose tissue infiltration decreases [56]. A shift in the distribution of the remaining macrophages was also observed, including two features: 1) disappearance of CLS, and 2) macrophages located near blood vessels [56]. The studies that investigated the impact of bariatric surgery on mRNA expression of total macrophage cell marker CD68 in abdominal subcutaneous AT and showed a significant CD68 mRNA expression levels were significantly decreased 12 and 24 months after bariatric surgery but not after 6 months [57–60].

Studies in rodents suggest that although subcutaneous ASCs derived from mice with partial weight loss present an improved proliferative ability, lipid accumulation was lower than in control differentiated ASCs. The inefficient lipid storage could indicate that after weight loss, ASCs do not recover the ability to differentiate

Study (authors, year)	Results regarding adipogenesis	Particularities (lot/study)
Mitterberger et al., 2014 [49]	Higher adipogenic differentiation rates for ASCs from former obese patients after significant lifestyle intervention weight loss;	Human subcutaneous ASCs from obese, OD (N = 4, BMI ≥ 30 kg/m^2), long-term calorically restricted initially obese, CRD (N = 4, former BMI ≥ 30 kg/m^2, current BMI ≤ 30) and normal weight, NWD (N = 4, BMI 19–25 kg/m^2).
Muir et al., 2017 [48]	A direct correlation between pre-bariatric subcutaneous ASC frequency and weight loss (12 month-%TWL);	Human subcutaneous ASCs from bariatric obese patients: diabetic, DM (BMI =46 kg/m2; N = 37); prediabetic PRE (BMI =48 kg/m^2; N = 26), and non-diabetic, NDM (BMI =46 kg/m^2; N = 32)
Silva et al., 2015 [50]	The ASCs from post-bariatric surgery ex-obese patients showed the highest levels of lipid accumulation whereas those from the obese women had the lowest levels. ASC behavior is altered in the subcutaneous adipose tissue of morbidly obese women; these changes are not completely restored after bariatric surgery-induced weight loss.	Human subcutaneous ASCs from bariatric obese women (N = 12, BMI = 46.2 ± 5.1 kg/m^2) and post bariatric surgery ex-obese women (N = 7, initial BMI = 47.8 ± 1.3 kg/m^2) and normal-weight women (N = 6, BMI = 27.5 ± 0.5 kg/m^2; final BMI = 28.1 ± 1.1 kg/m^2)

Table 2.
Relationship between subcutaneous ASCs and weight loss induced by surgical interventions.

to the adipocyte lineage. These studies indicate that reduced energy intake might create a protective environment [37].

Mitterberger et al. [49] provided evidence suggesting that long-term caloric restriction-induced by diet and bariatric surgery reduced DNA-damage, improved viability, extended replicative lifespan, and reduced adipogenic differentiation potential of subcutaneous ASCs in formerly obese women.

Muir et al. [48] observed a relationship between pre-surgical subcutaneous ASCs frequency and surgery-induced weight loss only in women, suggesting different sex-specific mechanisms of tissue remodeling associated with bariatric surgery weight loss responses. [48]. These findings indicate that the diagnosis of ASCs functions pre-bariatric surgery could predict the level of metabolic changes following bariatric surgery. This data would allow specialists to establish some criteria for the selection of obese patients with metabolic comorbidities for whom bariatric surgery would have the greatest benefit.

5. Diagnosis of abdominal subcutaneous ASC differentiation as a predictor of weight loss and metabolic outcome in bariatric patients

Large evidence indicates that enlargement of adipocytes in obesity is associated with low-grade chronic inflammation which further leads to abnormal adipokine release and impaired glucose metabolism [61]. In obese patients with associated diabetes mellitus, VAT contains larger adipocytes and fewer preadipocytes as compared to SAT [62]. However, studies that examined the relationship between generalized and regional adiposity and insulin sensitivity in type 2 diabetic patients concluded that upper-body SAT (abdominal) plays a major role in obesity-related insulin resistance in comparison to visceral or retroperitoneal fat. These results suggest that upper-body SAT had a stronger correlation with insulin sensitivity than VAT among type 2 diabetic men [16].

Studying the response to overfeeding in upper- and lower-body SAT, Tchoukalova et al. [63] reported the hypertrophy of upper-body (abdominal) adipocyte and hyperplasia of lower-body (gluteofemoral) adipocyte to overfeeding in healthy men. In morbidly obese women with normal plasma glucose concentrations, mean adipocyte volume was larger in VAT than that in SAT, but these two depots did not differ in the proportion of small adipocytes. The ability of metabolically healthy obese to expand lower-body fat is a protective mechanism involving a hyperplastic response to energy overload. High rates of adipogenesis were associated with a smaller size of abdominal subcutaneous adipocytes, lower waist-to-hip ratio, and more favorable metabolic profile [63].

In bariatric patients, the adipocyte size and the preadipocyte content were assessed in SAT (abdominal) and VAT (greater omentum) by Muir et al. [25]. They observed modest correlations between adipocyte size and weight loss only in VAT. Independently of adipocyte size, the surgery-induced weight loss (12 month-%TWL) was direct correlated with pre-surgical preadipocyte frequency only in female subjects and this correlation was more robust in SAT than VAT.

Recently, CT-derived radiodensity measurement has been validated against ex-vivo adipose tissue samples for the assessment of tissue lipid. In morbidly obese patients, lower CT-derived adipose tissue radiodensity (corresponding to higher lipid content) in abdominal fat depots was associated with metabolic disorders [64, 65]. The post-surgery increase in abdominal SAT and VAT radiodensities reflecting decreased lipid content, increased tissue blood flow rate, and diminishing adipose inflammation was associated with a favorable metabolic state.

There is a growing body of evidence to suggest that studying the abdominal subcutaneous ASCs differentiation using biopsies or adipose CT radiodensity is important to understand the tissue responses to weight loss. The diagnosis of the adipogenic potential of abdominal subcutaneous ASC could predict the weight-loss and metabolic outcome in obese patients following bariatric surgery.

6. Conclusions

Subcutaneous ASCs may be implicated in the variations of bariatric outcomes, through a different restoration in their proliferative and adipogenic potential. Weight loss induced by bariatric surgery correlates to the subcutaneous ASC functions and could explain the variability of metabolic improvement. Limited research data are available to the present and these data support the importance of diagnosis of subcutaneous ASCs functions as predictors of metabolic improvement after bariatric surgery.

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