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The Role of Adipose-Derived Stem Cell Dysfunction in the Transition from Obesity to Diabetes

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ABSTRACT

Adipose-derived stem cells (ADSCs), also called adipose stromal/stem cells, reside in the stromal vascular fraction of white adipose tissue and are essential for adipose tissue plasticity, healthy expansion and immunometabolic balance. In physiological states, ADSCs support adipocyte turnover, promote angiogenesis and exert immunoregulatory and anti-inflammatory actions, allowing subcutaneous fat to buffer caloric excess without provoking systemic insulin resistance.In obesity, however, chronic nutrient overload, hypoxia, oxidative stress and low-grade inflammation converge on ADSCs, driving senescence, epigenetic reprogramming, loss of proliferative capacity and skewed differentiation. Human and animal studies show that obesity and type 2 diabetes (T2D) are associated with early senescence and mitochondrial dysfunction in ADSCs, reduced clonogenicity and adipogenic potential, pro-fibrotic and pro-inflammatory secretomes and altered crosstalk with immune cells. These changes compromise adipose expandability, promote adipocyte hypertrophy, fibrosis and adipose inflammation and favor ectopic lipid deposition in liver and muscle, thereby accelerating the transition from obesity to insulin resistance and overt T2D. At the same time, ADSCs retain therapeutic potential: exogenous or rejuvenated ADSCs can ameliorate insulin resistance and β-cell dysfunction in preclinical diabetes models through anti-inflammatory and pro-regenerative mechanisms. This review synthesizes current evidence on how ADSC dysfunction contributes mechanistically to the obesity–diabetes transition, and discusses emerging strategies to preserve or restore ADSC function, including senescence-targeted interventions, niche modulation and cell-based therapies.

Keywords: adipose-derived stem cells; senescence; adipose plasticity; insulin resistance; type 2 diabetes

INTRODUCTION

Obesity does not inevitably lead to type 2 diabetes. Some individuals with substantial excess adiposity remain relatively insulin sensitive, while others progress rapidly to glucose intolerance and T2D despite similar body mass index[1–3]. A key determinant of this divergence is adipose tissue quality, particularly the ability of white adipose depots to remodel through hyperplasia rather than simple hypertrophy, to maintain adequate vascularization and to avoid excessive fibrosis and inflammation[4–7]. Adipose-derived stem cells sit at the core of this plasticity.

ADSCs are mesenchymal stromal cells resident in the stromal vascular fraction of adipose tissue. They display self-renewal, multipotent differentiation into adipocytes and other mesenchymal lineages, and paracrine capabilities that influence immune cells, endothelial cells and mature adipocytes[8–11]. In healthy adipose tissue, ADSCs replenish mature adipocytes, enabling controlled hyperplastic expansion in response to chronic caloric excess. Lineage-tracing and single-cell studies indicate that distinct ADSC subpopulations in subcutaneous and visceral depots give rise to depot-specific adipocytes and respond differentially to metabolic and inflammatory cues[12, 13].

This capacity for de novo adipogenesis is metabolically important. When new, small adipocytes are generated from progenitors, lipid storage is distributed across many cells with favorable surface area–to–volume ratios, preserving insulin sensitivity and limiting local hypoxia. By contrast, when progenitor proliferation and differentiation are constrained, existing adipocytes enlarge to accommodate excess lipid, predisposing to hypoxia, oxidative stress, macrophage recruitment and fibrotic remodeling[14, 15]. The "adipose expandability" concept posits that limited capacity of ADSCs to support healthy expansion is a tipping point at which obesity begins to drive systemic insulin resistance.

Beyond adipogenesis, ADSCs exert immunomodulatory and pro-regenerative effects. They secrete anti-inflammatory cytokines, growth factors and extracellular vesicles that can polarize macrophages toward M2-like phenotypes, support endothelial function and protect neighboring cells from oxidative and ER stress[16]. These properties underlie their appeal as a therapeutic cell source in regenerative medicine and, more recently, in metabolic disease. Experimental delivery of ADSCs in obese or diabetic rodents improves insulin sensitivity, reduces adipose and hepatic inflammation and can support β-cell survival and function[17].

However, obesity itself reshapes the biology of ADSCs in ways that undermine both their endogenous roles and their therapeutic utility. Human studies comparing ADSCs from lean and obese donors show that obesity is associated with reduced proliferative potential, early senescence, impaired differentiation capacity and altered secretory profiles[18]. Senescent ADSCs display cell-cycle arrest, DNA damage responses, mitochondrial dysfunction and a senescence-associated secretory phenotype enriched in pro-inflammatory and pro-fibrotic mediators[18]. These changes are driven by the obesogenic microenvironment, including chronic low-grade inflammation, lipotoxicity, hypoxia, reactive oxygen species and altered extracellular matrix composition, especially in visceral fat[18].

Dysfunctional ADSCs have at least three major consequences along the obesity–diabetes trajectory. First, reduced progenitor proliferation and adipogenesis limit healthy hyperplastic expansion, promoting adipocyte hypertrophy, adipose inflammation and insulin resistance at lower absolute fat masses[19]. Second, senescent, pro-inflammatory ADSCs reshape the adipose immune niche, supporting chronic macrophage activation and T-cell dysfunction that further impair insulin signaling in adipocytes[20]. Third, systemic spread of dysfunctional ADSC-derived extracellular vesicles and cytokines may influence liver, muscle and β-cells, contributing to ectopic fat, insulin resistance and β-cell stress[20].

The transition from uncomplicated obesity to T2D can thus be viewed, in part, as a failure of the adipose stem cell compartment. When ADSCs remain functionally robust, adipose tissue can expand and remodel in relatively "metabolically healthy" ways. When ADSCs become senescent, depleted or skewed toward fibrotic and inflammatory programs, adipose tissue loses its buffering capacity, and lipids and inflammatory signals spill over into other organs[21].

This review examines ADSCs as both guardians and potential saboteurs of metabolic health. Section 2 outlines ADSC biology in healthy adipose tissue. Section 3 describes obesity-induced ADSC dysfunction and senescence. Section 4 links ADSC failure to adipose tissue dysfunction and systemic insulin resistance. Section 5 discusses ADSC alterations in established T2D and their impact on regenerative and immunomodulatory potential. Section 6 reviews attempt to therapeutically target ADSCs or their niche. Section 7 highlights biomarker and research directions toward ADSC-focused strategies for preventing or delaying diabetes in obesity.

2. Biology of Adipose-Derived Stem Cells in Healthy Adipose Tissue

ADSCs are a major non-immune cell population within the stromal vascular fraction of white adipose tissue, particularly in visceral depots where they may constitute a substantial fraction of resident stromal cells[21]. They express canonical mesenchymal markers and depot-specific surface profiles and occupy specialized niches near vasculature, extracellular matrix and immune cells in what has been termed the adiponiche[22].

In homeostasis, ADSCs support adipocyte turnover. Mature adipocytes have limited proliferative capacity and must be replaced from progenitors. ADSCs can differentiate into preadipocytes and then into insulin-sensitive adipocytes that integrate into existing depots. This process is critical during growth, pregnancy and chronic positive energy balance, when demand for storage increases[22]. ADSCs also modulate the adipose microenvironment. They secrete vascular endothelial growth factor and other angiogenic factors that promote adequate vascularization during tissue expansion. They produce extracellular matrix components and remodeling enzymes that shape tissue architecture, enabling expansion without pathologic fibrosis. In addition, ADSCs exert immunomodulatory effects on macrophages, T cells and other immune cells, often skewing toward anti-inflammatory phenotypes under lean conditions[22].

Depot differences are important. Subcutaneous ADSCs generally favor adipogenic differentiation and are associated with more benign metabolic outcomes, whereas visceral ADSCs display transcriptional programs that predispose to pro-inflammatory and fibrotic remodeling[23]. This heterogeneity helps explain why visceral obesity is more tightly linked to T2D risk than subcutaneous fat accumulation. At the systemic level, the capacity of ADSCs to sustain hyperplastic adipose expansion underlies the concept of metabolically healthy obesity. Individuals whose ADSCs readily proliferate and differentiate in response to overnutrition can distribute lipid across many adipocytes, preserving insulin sensitivity and minimizing ectopic fat deposition[23]. Conversely, low proliferative potential and limited adipogenesis are associated with adipocyte hypertrophy, inflammation and insulin resistance at comparable degrees of obesity[23]. Thus, in healthy adipose tissue, ADSCs function as rheostats of adipose plasticity and immunometabolic tone. Their integrity is critical for maintaining a buffer between caloric excess and systemic metabolic deterioration.

3. Obesity-Induced ADSC Dysfunction: Senescence, Loss of Stemness and Niche Remodeling

Chronic obesity exposes ADSCs to a hostile milieu of elevated fatty acids and glucose, hypoxia, oxidative stress and pro-inflammatory cytokines. Over time, these factors drive a shift from youthful, multipotent ADSCs toward dysfunctional, senescent and pro-inflammatory states. Human and animal data indicate that obesity is associated with early senescence in ADSCs, marked by increased senescence-associated β-galactosidase activity, p16^INK4a and p21 expression, DNA damage markers and shortened telomeres[24]. Senescent ADSCs show reduced proliferative and clonogenic capacity and impaired adipogenic differentiation, often with a bias toward osteogenic or fibrogenic lineages[24].

The extracellular matrix and TGF-β signaling appear central in this process. Obesity-associated remodeling of the visceral adipose matrix, with increased stiffness and altered composition, promotes TGF-β–driven senescence and fibrotic programming in ADSCs. Pharmacologic blockade of TGF-β signaling in human visceral ADSCs can partially reverse senescence markers and restore functional properties in vitro, highlighting the role of the niche in dictating ADSC fate[24].

Inflammation further reprograms ADSCs. Exposure to obesity-associated cytokines and macrophage-derived signals drives transcriptional changes toward a senescence-associated secretory phenotype enriched in IL-6, IL-8, MCP-1 and matrix-remodeling enzymes[6, 25–27]. These secreted factors, in turn, reinforce local immune activation, attract monocytes and promote fibrotic remodeling, creating a feed-forward loop that deepens adipose dysfunction. Metabolic and mitochondrial alterations accompany these changes. Obese ADSCs exhibit impaired mitochondrial respiration, increased reactive oxygen species and altered lipid handling, which further fuel DNA damage and senescence pathways[28]. Epigenetic remodeling, including DNA methylation and histone modification changes linked to inflammatory and stress pathways, has also been documented and may encode a form of "metabolic memory" that persists even after weight loss[28, 29].

Collectively, obesity transforms ADSCs from flexible, reparative progenitors into exhausted, pro-inflammatory and pro-fibrotic cells with diminished adipogenic potential. This dysfunctional stem cell compartment reshapes the trajectory of adipose remodeling and sets the stage for systemic insulin resistance.

4. How ADSC Failure Drives Adipose Tissue Dysfunction and Systemic Insulin Resistance

ADSC dysfunction links obesity to insulin resistance through interconnected mechanisms in adipose tissue. When proliferative capacity and adipogenic potential decline, new adipocyte formation cannot keep pace with energy surplus. Existing adipocytes enlarge, particularly in visceral depots, leading to local hypoxia, oxidative stress and tissue stiffness[30].

Hypertrophic adipocytes are more insulin resistant and lipolytic, releasing greater amounts of free fatty acids and adipokines into the circulation. Elevated fatty acid flux to liver and skeletal muscle promotes ectopic fat accumulation and generation of lipotoxic intermediates such as diacylglycerols and ceramides that impair insulin signaling[30, 31]. At the same time, senescent ADSCs secrete pro-inflammatory cytokines and chemokines that recruit and activate macrophages and other immune cells. These immune cells further produce TNF-α, IL-1β and IL-6, amplifying local inflammation and directly inhibiting insulin signaling in adipocytes[31]. The adipose tissue becomes a chronic inflammatory organ, releasing deleterious signals systemically.

Fibrogenic skewing of ADSCs contributes to extracellular matrix deposition and fibrosis, particularly in visceral fat, which constrains tissue expandability and impairs perfusion. Fibrotic adipose tissue shows reduced plasticity and heightened vulnerability to lipotoxic and hypoxic injury, reinforcing the cycle of dysfunction[32]. Because ADSCs also regulate local immune balance, their dysfunction undermines the ability of adipose tissue to resolve inflammation. Loss of ADSC-mediated M2 macrophage polarization and Treg support favors sustained M1-dominant inflammation, which spills over into the systemic circulation via cytokines, adipokines and extracellular vesicles[32].

Thus, ADSC failure simultaneously reduces the structural capacity for safe lipid storage and distorts the immunometabolic environment of adipose tissue. The resulting hypertrophic, fibrotic and inflamed depots drive hepatic and muscular insulin resistance, setting the stage for hyperglycemia and T2D.

5. ADSC Dysfunction in Established Type 2 Diabetes: Consequences for Regeneration and Immunomodulation

T2D amplifies stress on ADSCs beyond that imposed by obesity alone. Chronic hyperglycemia, advanced glycation end products and further oxidative and ER stress exacerbate senescence and functional decline[33, 34]. Studies comparing ADSCs from obese individuals with and without T2D report additional impairments in proliferation, differentiation and paracrine function in the diabetic group, including reduced angiogenic and anti-inflammatory factor secretion[35].

This compounded dysfunction has two main implications. First, the endogenous capacity of adipose tissue to remodel toward a healthier phenotype is further compromised, making reversal of insulin resistance via weight loss alone more difficult and slower. Although substantial weight loss can reduce senescent cell burden in subcutaneous fat and partially rejuvenate adipose metabolism, residual inflammatory and fibrotic changes often persist, especially in visceral depots[36]. Second, ADSC dysfunction complicates the use of autologous ADSCs as a therapeutic modality in patients with obesity and T2D. While exogenous ADSC administration from healthy sources improves insulin sensitivity and β-cell function in animal models, ADSCs harvested from obese or diabetic donors show reduced stemness, altered secretomes and sometimes pro-inflammatory tendencies, raising concerns about their efficacy and safety in autologous transplantation[37].

Despite these challenges, carefully characterized and possibly preconditioned ADSCs from diabetic subjects may retain therapeutic potential. In vitro conditioning, genetic modification or senolytic treatment to reduce senescent cell content are being explored to restore more youthful phenotypes[37]. Understanding how T2D alters ADSC biology is therefore essential both for interpreting endogenous adipose behavior and for designing safe and effective cell-based interventions.

6. Therapeutic Strategies Targeting ADSCs and Their Niche

Given their central role in adipose plasticity and immunometabolism, ADSCs are attractive therapeutic targets in obesity-related diabetes, both as cells to protect and as tools to deploy.

Lifestyle and surgical interventions that induce weight loss are the most fundamental means of improving ADSC health. Bariatric surgery and intensive lifestyle programs reduce adipose inflammation and senescent cell burden and can reprogram adipose transcriptomes toward more youthful states, likely including ADSCs, although direct single-cell data on ADSCs are only beginning to emerge[38]. Pharmacologic modulation of the ADSC niche is another avenue. Targeting TGF-β signaling, which drives obesity-induced ADSC senescence and fibrogenic skewing, has shown promise in restoring proliferative and adipogenic capacity in human visceral ADSCs ex vivo[38]. More broadly, anti-inflammatory and anti-fibrotic agents that improve adipose tissue quality may secondarily rejuvenate ADSCs. GLP-1 receptor agonists, SGLT2 inhibitors and thiazolidinediones all remodel adipose tissue and reduce inflammation; whether they directly benefit ADSCs remains an active area of investigation.

Direct ADSC-based therapies have shown efficacy in experimental T2D. Systemic or local delivery of ADSCs in diabetic rodents improves insulin sensitivity, reduces adipose and hepatic inflammation, supports β-cell survival and improves microvascular complications, largely via paracrine mechanisms that modulate macrophage polarization and inflammasome activation[39]. Allogeneic ADSCs from healthy donors may circumvent some limitations of autologous ADSCs from obese or diabetic patients, but raise immunologic and regulatory questions. Senescence-targeted strategies are emerging as a promising adjunct. Senolytic drugs that selectively eliminate senescent cells, or senomorphic agents that blunt the senescence-associated secretory phenotype, have the potential to reduce the burden of dysfunctional ADSCs and restore niche function[40]. However, preserving beneficial progenitors while removing harmful senescent cells will require precise targeting.

Finally, exosomes and other extracellular vesicles derived from healthy ADSCs are being explored as cell-free therapies, delivering regenerative and immunomodulatory cargo without the risks associated with live-cell transplantation. Early studies suggest that ADSC-derived vesicles can improve insulin sensitivity and reduce inflammation in preclinical models, although their interaction with endogenous, obesity-altered EV networks must be carefully considered[40].

7. Biomarkers, Open Questions and Future Directions

Despite rapid progress, many questions remain about how ADSC dysfunction shapes the obesity–diabetes transition and how best to exploit this knowledge clinically. On the biomarker front, there is interest in identifying circulating or tissue markers that reflect ADSC health, such as senescence-associated transcripts in adipose biopsies, ADSC-derived extracellular vesicle signatures or depot-specific progenitor cell profiles from single-cell RNA sequencing[41]. Such markers could help identify individuals whose adipose stem cell compartment is failing, and who may be at particularly high risk of progressing from obesity to T2D, even at moderate BMI[42].

Mechanistically, disentangling cause and effect remains challenging. Obesity-induced ADSC senescence clearly correlates with adipose dysfunction and insulin resistance, but the precise contribution of ADSC decline relative to changes in mature adipocytes, immune cells, and vasculature is still being defined. New models that allow selective manipulation of ADSC function, senescence, and fate in vivo will be critical to establish causality[41].

Therapeutically, the feasibility of targeting ADSCs in humans will depend on balancing benefits and risks. Strategies that broadly stimulate ADSC proliferation or adipogenesis could, in theory, exacerbate weight gain or promote tumorigenesis if not carefully controlled. Conversely, aggressive senolytic approaches might deplete essential progenitor pools if specificity is insufficient[43].

Future directions include integrating ADSC-focused metrics into clinical trials of obesity and T2D therapies to determine how various interventions influence the stem cell compartment and whether such changes predict long-term metabolic outcomes. Precision approaches might eventually stratify patients by ADSC health and adipose plasticity, guiding decisions about the intensity and type of intervention needed to prevent diabetes[43].

CONCLUSION

In summary, adipose-derived stem cells are central architects of adipose tissue structure and function. Their dysfunction in obesity through senescence, loss of stemness, and pro-inflammatory reprogramming undermines adipose plasticity and accelerates the spillover of lipids and inflammatory signals that drive systemic insulin resistance and type 2 diabetes. Understanding, monitoring, and ultimately correcting ADSC dysfunction offers a promising, mechanistically grounded path to interrupt the transition from obesity to diabetes, shifting care from late-stage glycemic control to earlier preservation of adipose health.

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