

Adipose tissue dysfunction under inflammatory conditions and possibilities for its correction using cell therapy



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ABSTRACT

Adipose tissue dysfunction under inflammatory conditions is a key pathogenetic factor in the development of metabolic and systemic disorders, including systemic inflammatory response syndrome (SIRS) and chronic inflammatory processes. This review summarizes current clinical and experimental evidence on the functional, morphological, and molecular alterations in adipose tissue under acute and chronic inflammation.

The data indicate that inflammatory conditions disrupt the secretory activity of adipocytes and adipose tissue-derived mesenchymal stromal cells (MSCs), leading to increased production of pro-inflammatory cytokines, chemokines, and other mediators. The resulting pro-inflammatory microenvironment adversely affects MSCs, reducing their proliferative and differentiation capacity, impairing regenerative potential, and causing telomere shortening associated with cellular aging. The role of immune cells, particularly macrophages, in sustaining chronic inflammation and promoting adipose tissue dysfunction is also highlighted.

Special attention is given to current strategies for mitigating inflammation-induced adipose tissue alterations using cell-based therapy. MSCs, due to their immunomodulatory, anti-inflammatory, and regenerative properties, represent a promising approach for restoring adipose tissue homeostasis and alleviating systemic inflammation.

CONCLUSIONS. *Acute and chronic inflammation induces profound changes in adipocyte and MSC function, impairing the regulatory and reparative capacity of adipose tissue. MSC-based therapy holds potential for correcting adipose tissue dysfunction under inflammatory conditions, but further studies are needed to elucidate mechanisms of action, optimize treatment protocols, and evaluate long-term safety and efficacy.*

KEY WORDS: *systemic inflammatory response syndrome; chronic inflammation; adipose tissue; adipose-derived mesenchymal stromal cells; immunomodulation; cell therapy*

Inflammation is a multilevel biological response of the organism to tissue injury, aimed at protection against harmful stimuli and initiation of the healing process. Two main types of inflammation are distinguished: acute inflammation, characterized by a rapid onset, pronounced clinical manifestations, and a short duration lasting from several days to weeks; and chronic inflammation, which develops slowly, persists for prolonged periods (months or years), and often has a latent course.

In most cases, inflammation resolves rapidly; however, in the presence of certain factors – either infectious (bacterial, viral, or fungal infections) or non-infectious (burns, trauma, pancreatitis, ischemia, autoimmune diseases, etc.) – the inflammatory process may lead to severe systemic manifestations with the development of an acute systemic inflammatory response. If the initial trigger is not eliminated and continues to act, acute

inflammation may progress to a chronic state. Persistent low-grade inflammation is a major underlying cause of cardiovascular diseases, type 2 diabetes mellitus, insulin resistance, certain types of cancer, metabolic syndrome, and other pathological conditions associated with obesity, physical inactivity, and physiological aging [1, 2].

Studies conducted over the past two decades have demonstrated that adipose tissue can serve as a substrate for obesity-associated inflammation. Excess lipid accumulation in adipose tissue leads to its dysfunction, which is characterized by chronic inflammation, hypoxia, and fibrosis. Under hypoxic conditions, numerous immune cells become activated. In particular, macrophages release pro-inflammatory cytokines that exert systemic effects on the entire organism, thereby inducing or exacerbating inflammatory processes [3].

Disruption of the balance between lipogenesis and lipolysis transforms adipose tissue from a safe energy storage depot into a source of pro-inflammatory mediators, which may contribute to the maintenance of chronic inflammation and, consequently, to the development of metabolic syndrome [4, 5]. Inflammation of adipose tissue against the background of impaired energy metabolism and hormonal dysregulation may manifest in the formation of painful nodules, fibrotic scars, and fistulas [6]. All these pathological processes are closely related to the structural and functional characteristics of adipose tissue.

Structural characteristics of adipose tissue

Adipose tissue is a specialized type of connective tissue composed of highly differentiated cells – adipocytes – that accumulate lipids in the form of cytoplasmic lipid droplets. When caloric demand increases, adipose tissue mobilizes stored lipids into the bloodstream, thereby serving as an energy source for peripheral tissues. In this way, adipose tissue performs its primary function as a key regulator of energy storage and expenditure in the organism.

Adipose tissue is conventionally classified into brown adipose tissue and white adipose tissue. Brown adipose tissue is predominantly present in neonates and gradually decreases with age. A defining feature of brown adipose tissue is the presence of numerous small lipid droplets and a high density of mitochondria within the adipocyte cytoplasm, which are essential for non-shivering thermogenesis and contribute to protection against hypothermia in infants. The high iron content of mitochondria confers the characteristic brown coloration to this tissue.

The majority of adipose tissue in adults is represented by white adipose tissue, which is widely distributed throughout the human body and, depending on anatomical localization, is subdivided into subcutaneous adipose tissue – located between the skin and underlying musculature – and visceral adipose tissue, which is associated with internal organs. Visceral adipocytes are characterized by their relatively large size (particularly in obesity), the presence of a single large lipid droplet that displaces the nucleus toward the cell periphery, and a pronounced endocrine activity, which contributes to the development of metabolic disturbances through active hormone secretion [7].

In the context of obesity, adipocytes within visceral adipose tissue acquire pro-inflammatory properties and can promote systemic inflammation by recruiting and activating immune cells, particularly macrophages, followed by the release of inflammatory cytokines and adipokines, ultimately contributing to the development of chronic diseases [8]. In contrast, subcutaneous adipose tissue is considered more metabolically inert and consists of adipocytes containing fewer mitochondria and a single lipid droplet, favoring energy storage rather than energy dissipation through thermogenesis [9].

The anatomical distribution of adipose tissue in humans is closely associated with insulin resistance. A meta-analysis by Zhang M. et al. demonstrated that visceral fat mass shows a strong positive correlation with insulin resistance, exceeding that of conventional obesity indicators such as body mass index (BMI) and waist circumference. These findings suggest that fat distribution is a more critical determinant of metabolic health than total fat mass [10].

Adipose tissue possesses a unique capacity to expand and contract in both volume and mass without proportional changes in other tissues. For example, with an increase in body weight from 70 to 150 kg, adipose tissue mass may increase approximately fourfold relative to bone or muscle mass. According to data reported by Spalding et al., the total number of adipocytes remains relatively constant during adulthood in both lean and obese individuals, even following substantial weight loss. Variations in adipose tissue mass are largely attributable to changes in lipid accumulation. To accommodate these dynamic fluctuations, adipose tissue undergoes expansion or reduction primarily through changes in adipocyte size (hypertrophy) rather than cell number. This indicates that adipocyte number is largely established during childhood and adolescence, whereas total fat mass in adulthood is regulated predominantly by alterations in adipocyte volume rather than adipocyte hyperplasia [11].

Excess caloric intake leads to increased storage of triglycerides within adipocytes, resulting in cellular hypertrophy and the development of visceral obesity. In individuals with both elevated and normal BMI, increased visceral fat content is associated with a higher prevalence of metabolic syndrome. The pathophysiological link between visceral obesity and metabolic syndrome is mediated, at least in part, by a systemic inflammatory response [12–15].

Adipose tissue and acute systemic inflammation

Adipose tissue is no longer considered merely an inert energy storage depot. In addition to its thermoregulatory and energy storage functions, adipose tissue exhibits properties of an endocrine organ, producing hormones, cytokines, and other bioactive factors. These adipokines influence appetite regulation, metabolism, insulin sensitivity, the course of inflammatory processes, and immune responses. Through the secretion of biologically active mediators, adipose tissue participates in complex regulatory networks, modulating the function of the brain, vascular system, and other organs and systems of the body [16].

Adipose tissue dysfunction, particularly in the context of obesity, may contribute to the development of systemic inflammatory response syndrome (SIRS) through the release of pro-inflammatory cytokines and chemokines. These factors promote the recruitment and activation of immune cells, primarily macrophages, thereby sustaining chronic low-grade inflammation that disrupts insulin signaling, induces oxidative stress, and ultimately leads to metabolic dysfunction [17]. SIRS is characterized by an excessive immune response to infectious or non-infectious insults. At the molecular level, two major categories of SIRS triggers are distinguished [18]:

- Damage-associated molecular patterns (DAMPs), which are released in response to extensive tissue injury (e.g., polytrauma, severe burns, acute pancreatitis, postoperative conditions, ischemia and organ necrosis, autoimmune exacerbations, toxic reactions to substances, etc.);
- Pathogen-associated molecular patterns (PAMPs), which arise from pathogenic microorganisms, including viruses, bacteria, and fungi.

Following exposure to a damaging stimulus, injured tissues release various DAMP-related molecules, such as high-mobility group box 1 protein (HMGB1), adenosine triphosphate (ATP), and nuclear components, including histones and mitochondrial DNA. Among DAMPs are endogenous ligands such as saturated fatty acids (SFAs), modified low-density lipoproteins (LDL), advanced glycation end products, extracellular matrix degradation products, and heat shock proteins. These molecules are recognized by Toll-like receptors (TLRs), particularly TLR2 and TLR4, leading to activation of pro-inflammatory signaling cascades [19].

Conversely, invading bacteria or their PAMPs, such as lipopolysaccharide (LPS), can further amplify the inflammatory response by recruiting immune cells. Neutrophils and monocytes/macrophages are among the first responders to such stimuli and subsequently produce a wide array of cellular mediators, including interleukins (IL-1, IL-6, IL-8), interferon-gamma (IFN- γ), and tumor necrosis factor-alpha (TNF- α), as well as generate reactive oxygen species (ROS) [20, 21].

Overall, inflammation induced by infectious or non-infectious factors involves a complex interplay between humoral and cellular immune responses, cytokine networks, and the complement system. The pathogenetic mechanisms of SIRS are primarily aimed at eliminating the injurious agent and promoting tissue repair. However, in cases of dysregulated or decompensated responses, SIRS may lead to reversible or irreversible organ dysfunction. Key factors that increase the risk of developing SIRS in response to harmful stimuli include advanced age (≥ 65 years), immunosuppression (e.g., cytostatic therapy or HIV infection), diabetes mellitus, and obesity [22].

Ultimately, SIRS develops when the balance between pro-inflammatory and anti-inflammatory cascades shifts towards excessive inflammation. Cytokines, particularly IL-6, stimulate the production of acute-phase reactants such as C-reactive protein (CRP). To counteract

this pro-inflammatory state, the organism activates a regulatory mechanism known as the compensatory anti-inflammatory response syndrome (CARS). This response is characterized, among other features, by increased production of IL-4 and IL-10, which suppress the synthesis of TNF- α , IL-1, IL-6, and IL-8 [23].

Excessive release of cytotoxic immune mediators, including reactive oxygen species and proteases, together with nonspecific immune activation and sustained inflammation, leads to endothelial dysfunction. Endothelial dysfunction plays a central role in the pathogenesis of SIRS, as the endothelium is a key regulator of coagulation balance, vascular tone, capillary permeability, and selective transendothelial leukocyte migration. Disruption of endothelial homeostasis compromises tissue integrity throughout the body and may ultimately result in multiple organ dysfunction syndrome (MODS) [24, 25].

According to published studies, concentrations of pro-inflammatory cytokines such as IL-6, IL-8, and TNF- α are elevated in adipose tissue following traumatic injury, including bone fractures [26]. Even minimally invasive procedures, such as catheter insertion into the paraumbilical region for lipoaspirate collection, have been shown to increase levels of inflammatory cytokines IL-1 β , IL-6, CXCL8 (IL-8), and TNF- α in human adipose tissue [27]. In animal models, burn injury has been associated with increased expression of inflammatory marker mRNAs, including IL-6, IL-8, MCP-1, and TNF- α , in adipocytes of subcutaneous adipose tissue [28].

A clinical study by Saraf M.K. et al. demonstrated elevated levels of IL-6, IL-8, TNF- α , IL-1 α , and IL-1 β in the subcutaneous adipose tissue of pediatric burn-injured patients compared with healthy controls. Histological analysis of adipose tissue samples from burn-injured children revealed reduced adipocyte size and increased collagen content relative to controls. Notably, enhanced collagen deposition was observed both intracellularly and within the extracellular matrix, indicating pronounced fibrosis of subcutaneous adipose tissue in burn-injured children. Electron microscopy further revealed the presence of multiple lipid droplets and an increased number of mitochondria, while immunohistochemical analysis demonstrated a marked accumulation of macrophages. In contrast, macrophages were absent or only sporadically detected in adipose tissue from healthy children [29].

Thus, SIRS represents a universal systemic response to trauma, infection, or burn injury. While it may initially manifest as an acute condition, prolonged exposure to damaging factors or ineffective therapeutic intervention can result in its progression to chronic inflammation.

Adipose tissue and chronic inflammation

Adipose tissue plays a central role in the development of chronic systemic inflammation through the release of pro-inflammatory cytokines that initiate a cascade of reactions leading to fever, tachycardia, alterations in leukocyte profiles, and an increased risk of multiple organ dysfunction. Preclinical and clinical studies demonstrate that chronic low-grade inflammation of adipose tissue, in contrast to classical acute and transient innate immune responses, is strongly associated with metabolic diseases and organ-related complications in the context of overweight and obesity [30, 31].

The capacity of adipocytes to uptake excess triglycerides is limited; when energy storage becomes excessive, the organism responds by generating new adipocytes [32]. Progressive increases in both adipocyte size and number may outpace the development of adequate vascularization, resulting in reduced blood supply, hypoxia, necrosis, and macrophage infiltration. These processes disrupt adipose tissue homeostasis, promote insulin resistance, and initiate inflammatory responses. Increased energy expenditure mobilizes triglycerides from adipocytes, which are hydrolyzed into glycerol and free fatty acids and subsequently released into the circulation. These lipids infiltrate peripheral organs, including skeletal muscle, liver, and visceral adipose tissue, exerting lipotoxic effects that contribute to chronic low-grade inflammation and metabolic dysfunction [33, 34].

Using various dietary models in immunocompromised mice, Lee Y. et al. demonstrated the critical role of chronic inflammation in the development of insulin resistance and obesity following prolonged consumption of a Western-style diet, characterized by high contents of refined sugars, salt, white flour, processed meats, and purified animal fats [35]. Intake of such diets leads to rapid caloric overload, sharp postprandial increases in plasma glucose and insulin levels, and enhanced nutrient uptake by adipose tissue, thereby promoting accelerated weight gain.

Under these conditions, adipocytes secrete a wide range of adipokines that play pivotal roles in the pathogenesis of insulin resistance and metabolic syndrome. These include hormones (leptin, adiponectin), peptides (angiotensinogen, apelin, resistin, and plasminogen activator inhibitor-1 (PAI-1)), as well as pro-inflammatory cytokines (IL-6, TNF- α , visfatin, omentin, and chemerin) [36].

Leptin is considered a key obesity-associated factor in metabolic syndrome, with elevated circulating levels correlating positively with increased inflammation. Leptin is known to promote pro-inflammatory immune responses through activation of the T helper 1 (Th1) pathway [37]. In contrast, adiponectin enhances insulin sensitivity and exerts anti-inflammatory effects, in part by modulating the nuclear factor kappa B (NF- κ B) signaling pathway [38]. Clinical studies have demonstrated reduced adiponectin levels in patients with diabetes mellitus compared with healthy controls, supporting a protective role for adiponectin against the development and progression of insulin resistance [39].

Recently, increasing attention has been focused on chemerin, an adipocyte-derived chemoattractant. Studies using animal models and cell cultures have confirmed its involvement in glucose metabolism, adipogenesis, angiogenesis, and the regulation of chronic inflammation [40]. Several clinical studies have reported significantly elevated circulating chemerin levels in individuals diagnosed with metabolic syndrome [41].

Adipose tissue also produces the peptide angiotensin II, the plasma concentration of which is increased in obesity and insulin resistance [42]. Angiotensin II activates NADPH oxidase, leading to enhanced production of reactive oxygen species. ROS exert multiple pleiotropic effects, including endothelial damage, platelet aggregation, increased NF- κ B expression, and oxidation of LDL [43, 44].

Thus, adipose tissue – particularly in the setting of obesity – serves as a major source of chronic low-grade inflammation. Enhanced secretion of pro-inflammatory cytokines combined with reduced production of protective adiponectin under these conditions promotes insulin resistance, metabolic disturbances, and joint-related complications. Consequently, persistent adipose tissue inflammation increases the risk of numerous severe diseases, including cardiovascular and malignant disorders, as chronic inflammation exerts profound systemic detrimental effects on virtually all organ systems.

Adipose tissue in metabolic syndrome

Dysfunction of adipose tissue is closely associated with the key pathogenetic mechanisms underlying metabolic syndrome (MetS). Metabolic syndrome represents a cluster of metabolic abnormalities, including insulin resistance, atherogenic dyslipidemia, central obesity, and hypertension. The pathogenesis of MetS is driven by a complex interplay of genetic and epigenetic factors, while overeating and physical inactivity are considered major environmental contributors to its development [45].

Innate immune receptors, particularly TLRs, play an active role in the inflammatory processes associated with metabolic syndrome, as demonstrated in both animal and human studies [46, 47]. TLRs are widely expressed and highly conserved transmembrane receptors that may represent critical determinants of weight gain and its metabolic consequences. They recognize conserved molecular patterns associated with pathogens (pathogen-associated molecular patterns, PAMPs) derived from bacteria, viruses, fungi, and parasites, as well as endogenous damage-associated molecular patterns (DAMPs) released during cellular injury, thereby initiating innate immune responses. Acting as molecular

“sensors” of microbial and endogenous danger signals, TLRs activate intracellular signaling pathways that culminate in cytokine production and immune cell activation.

In mice with high-fat diet-induced metabolic syndrome, increased expression and activity of TLR4 have been reported [48]. In a dietary intervention study using two distinct diets – one enriched with ω -6 polyunsaturated fatty acids and sucrose, and another rich in saturated fats and sucrose supplemented with cholesterol – conducted in male wild-type C57Bl/6 Hsd mice and TLR2-deficient (Tlr2^{-/-}) mice, the role of TLR2 in obesity and metabolic syndrome development was evaluated. TLR2-deficient mice were largely protected against diet-induced obesity, insulin resistance, hypercholesterolemia, and dyslipidemia. Deletion of the Tlr2 gene in adipose tissue was associated with reduced adipocyte hypertrophy, decreased macrophage infiltration, and lower expression of inflammatory cytokines [49].

In humans with metabolic syndrome, significantly increased expression of both TLR2 and TLR4 has been observed on the surface of circulating monocytes. This excessive activation of innate immune pathways correlates with elevated levels of endogenous activators (such as free fatty acids, oxidized low-density lipoproteins, and lipopolysaccharide-binding protein) as well as exogenous ligands (LPS) in these patients [50, 51]. Increased circulating bacterial endotoxin levels – classical ligands for TLR4 – are attributed to enhanced intestinal permeability in individuals with gut microbiota dysbiosis associated with metabolic syndrome [52].

Chronic inflammation in metabolic syndrome is accompanied by elevated levels of pro-inflammatory markers, including IL-6, CRP, and TNF- α . IL-6 is secreted by both macrophages and adipocytes [53]. Studies indicate that IL-6 stimulates hepatic CRP production, and circulating CRP levels strongly correlate with type 2 diabetes mellitus and metabolic syndrome [54]. IL-6 also affects vascular smooth muscle cells and endothelial cells by promoting the expression of vascular cell adhesion molecules (VCAMs) and activating the local renin-angiotensin system, thereby contributing to vascular inflammation, endothelial dysfunction, and atherosclerosis. Collectively, these processes lead to a pro-inflammatory tissue environment and progressive fibrosis during metabolic syndrome progression [55].

TNF- α is produced primarily by macrophages residing in adipose tissue, and its expression increases proportionally with adipose tissue mass. TNF- α levels correlate strongly with insulin resistance – one of the defining features of metabolic syndrome. TNF- α impairs insulin signaling in adipocytes and hepatocytes through serine phosphorylation and inactivation of insulin receptor substrates, thereby reducing the metabolic effects of insulin [56].

During metabolic syndrome development, adipocytes undergo distinct morphological alterations. Adipose tissue characterized by a relatively small number of large adipocytes exhibits hypertrophic morphology, whereas tissue composed of numerous smaller adipocytes demonstrates hyperplastic characteristics. According to Tchernof et al., subcutaneous adipocytes in overweight women were significantly larger than visceral adipocytes [57].

Fang L. et al. reported that the mean adipocyte size in subcutaneous fat was significantly greater than that in omental or mesenteric fat depots in individuals with type 2 diabetes compared with non-diabetic controls. In both subcutaneous and omental fat depots, a significant increase in the proportion of small adipocytes and a corresponding decrease in large adipocytes were observed in diabetic individuals. Similar trends were noted in mesenteric fat, with a significant reduction in the diameter of small adipocytes in the diabetic group [58].

A strong correlation has been identified between increased mean size of subcutaneous adipocytes and metabolic disturbances such as hyperinsulinemia and glucose intolerance associated with insulin resistance. Hoffstedt et al. demonstrated that increased visceral adipocyte volume in women was significantly associated with elevated plasma levels of apolipoprotein B, total cholesterol, LDL cholesterol, and triacylglycerols. In contrast, enlargement of subcutaneous adipocytes correlated primarily

with plasma insulin and glucose levels. Notably, a higher proportion of small adipocytes (indicative of hyperplasia) in both visceral and subcutaneous depots was associated with more favorable glucose, insulin, and lipid profiles compared with hypertrophic adipocyte expansion [59].

Veilleux et al. showed that women with varying degrees of obesity exhibited significantly higher plasma levels of triacylglycerols, very-low-density lipoproteins, and LDL cholesterol, which were associated with hypertrophic changes in omental visceral adipocytes, compared with women displaying hyperplastic adipose tissue morphology [60].

McLaughlin T. et al. reported no significant sex-related differences in the proportion of small adipocytes among obese individuals; however, the total number of adipocytes was significantly higher in men. Although no difference in total adipocyte number was observed between insulin-resistant and insulin-sensitive subgroups, the proportion of large adipocytes was significantly lower and the ratio of small-to-large adipocytes was significantly higher in insulin-resistant individuals. Additionally, both the proportion of small adipocytes and the diameter of large adipocytes were increased in the insulin-resistant subgroup compared with insulin-sensitive individuals [61].

According to Lönn M. et al., women with type 2 diabetes mellitus exhibited significantly larger subcutaneous adipocytes than healthy controls, with adipocyte hypertrophy closely correlating with multiple metabolic disturbances related to insulin resistance [62]. Consistently, Pasarica M. reported that in patients with type 2 diabetes, large subcutaneous adipocytes were approximately 67 % larger, whereas small adipocytes were approximately 20 % smaller compared with BMI-matched obese individuals without diabetes. Importantly, the total number of adipocytes was lower in patients with type 2 diabetes, while the proportion of small adipocytes was 27 % higher. These findings suggest that in type 2 diabetes, adipocyte number does not adequately increase in response to expanding fat mass, potentially leading to ectopic lipid accumulation in visceral adipose tissue, skeletal muscle, and liver, thereby exacerbating insulin resistance [63].

Visceral obesity represents one of the principal drivers of metabolic syndrome development. The pathophysiological link between visceral adiposity and metabolic syndrome is mediated by cytokines produced by visceral adipose tissue that impair insulin sensitivity, including TNF- α , IL-6, and IL-1 β . Elevated levels of non-esterified free fatty acids released from visceral fat further promote insulin resistance through activation of TLR4 signaling, accumulation of diacylglycerols, and ceramide synthesis [64].

Even in individuals with normal body weight, the risk of metabolic syndrome increases when visceral fat area exceeds 100 cm² as assessed by computed tomography (CT). In a longitudinal study involving 398 individuals with normal BMI followed for six years, Sun Y. et al. demonstrated a nonlinear positive association between visceral fat area and metabolic syndrome risk, with a threshold value of 100 cm². Visceral fat areas exceeding 162.85 cm² were identified as a robust and effective predictor of metabolic syndrome in this population [65]. Similarly, Lee A. et al. reported that visceral adipose tissue exhibited higher predictive value for metabolic syndrome risk than waist circumference or BMI among individuals with normal body weight [66].

At the same time, individuals with normal body weight typically exhibit superior metabolic adaptability, enabling effective weight maintenance and reduced risk of obesity-related disorders. As metabolic rate declines with aging, lifestyle modifications become increasingly important to prevent visceral fat accumulation and delay the onset of metabolic syndrome [67].

Collectively, these findings demonstrate that morphological alterations in adipocytes of both subcutaneous and visceral adipose tissue are closely associated with systemic metabolic disturbances. Body weight gain primarily occurs through changes in adipocyte volume. The development of insulin resistance is associated with both an increased proportion of small adipocytes and hypertrophy of large adipocytes. However, whether increased mean adipocyte size represents a cause or a consequence of insulin resistance remains unresolved and requires further investigation into the physiological and genetic mechanisms regulating adipocyte size [68].

Adipose tissue dysfunction and stem cells

Among the numerous sources of multipotent mesenchymal stromal cells (MSCs), adipose tissue-derived stem/stromal cells (AD-MSCs) have emerged as an attractive tool in clinical research due to their easy accessibility, low immunogenicity, high proliferative capacity, and multipotency. Typically, AD-MSCs are obtained after *in vitro* expansion of the stromal vascular fraction (SVF) isolated from adipose tissue by liposuction or during open surgical procedures. Both autologous and allogeneic AD-MSCs are currently used in clinical trials. In contrast to bone marrow-derived MSCs, AD-MSCs exhibit a more pronounced immunomodulatory effect but a longer replication period. It is well established that the proliferative and differentiation potential of AD-MSCs declines with age. In addition, the presence of diabetes mellitus, increased body mass index, and exposure to radiation are factors that significantly affect the morphofunctional properties of these cells [69].

In vitro studies demonstrate that AD-MSCs derived from subcutaneous adipose tissue possess a significantly higher adipogenic potential compared with AD-MSCs isolated from visceral adipose tissue, resulting in the formation of more functional and better organized adipocytes. Adipocytes differentiated from subcutaneous AD-MSCs exhibit a greater capacity for adiponectin secretion and a reduced tendency toward lipolysis [70, 71].

MSCs exert systemic immunomodulatory effects through the release of extracellular vesicles (EVs) [72]. It has been shown that microRNAs and mRNAs contained within EVs isolated from the conditioned medium of cultured porcine adipose-derived stem cells regulate the activity of transcription factors in recipient cells, as well as proteins capable of modulating cellular pathways involved in tissue repair and regeneration [73].

Numerous studies indicate that AD-MSCs possess potent immunomodulatory properties mediated through direct cell–cell interactions and paracrine mechanisms, including the production of cytokines and various soluble factors that regulate immune cell functions, improve the tissue microenvironment for wound healing, and exert strong immunosuppressive effects by reducing the production of inflammatory cytokines. Adipose-derived stem cells are considered more powerful suppressors of immune responses than MSCs derived from other tissue sources, such as bone marrow, dental pulp, and umbilical cord tissue [74].

However, dysfunction at the level of adipose tissue inevitably affects the properties of resident MSCs, which may negatively impact their regenerative potential. Metabolic disturbances impair the stemness of MSCs, as evidenced by telomere shortening, decreased expression of the proliferation marker Ki-67, and enhanced apoptosis resulting from DNA damage [75]. AD-MSCs obtained from patients with pathological obesity exhibit reduced expression of two fundamental transcription factors – T-box 15 (TBX15) and Homeobox C10 (HOXC10) – as well as ACTA2, a marker of AD-MSCs. Decreased expression of these factors indicates that obesity interferes with the multipotency of AD-MSCs. In addition, significant upregulation has been observed in genes involved in commitment to the adipocyte lineage or regulation of adipogenesis, including transcription factor 21 (TCF21), paired-like homeodomain transcription factor 2 (PITX2), leukemia inhibitory factor (LIF), osteoprotegerin (TNFRSF11B), and hyaluronan and proteoglycan link protein 1 (HAPLN1). In contrast, expression of RUNX2 (Runt-related transcription factor 2), which promotes osteoblastogenesis, is reduced compared with that in AD-MSCs from healthy individuals [76].

Under conditions of metabolic syndrome, the anti-inflammatory capacity of MSCs is diminished. According to Silva K. et al., subcutaneous AD-MSCs from obese patients promoted increased secretion of pro-inflammatory cytokines, including IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) [77]. Other studies have reported elevated expression of pro-inflammatory molecules in AD-MSCs from obese patients, such as IL-1 β , IL-8, MCP-1, and oxidized low-density lipoprotein receptor 1 (OLR1). In contrast, expression of death-associated protein kinase 1 (DAPK1) was reduced in AD-MSCs from obese individuals compared with cells from control subjects [76]. Furthermore, MSCs derived from both visceral and subcutaneous adipose tissue of patients with metabolic syndrome exhibit a reduced capacity to form vascular-like

tubular structures compared with stem cells from individuals without metabolic syndrome, which is attributed to decreased VEGF secretion during adipogenic differentiation [78].

According to the study by Barbagallo I. et al., AD-MSCs obtained from patients with type 2 diabetes mellitus exhibit a lack of expression of adipogenic differentiation markers compared with stem cells obtained from healthy donors, indicating an impaired ability of diabetic AD-MSCs to differentiate into adipocytes. In addition, IL-1 β gene expression was significantly higher in AD-MSCs from diabetic patients compared with MSCs from healthy individuals. Conversely, following differentiation, IL-1 β expression increased in AD-MSCs from healthy donors, whereas it remained reduced in AD-MSCs obtained from patients with diabetes [79].

Given the well-established negative impact of systemic inflammation on the functional characteristics and regenerative potential of MSCs, the issue of selecting an optimal donor source for autologous or allogeneic cell therapy becomes particularly relevant. Although endogenous MSCs are capable of activation under conditions of an abnormal microenvironment – such as hypoxia, inflammatory, and apoptotic signals – during polytrauma or infections associated with SIRS, their tissue abundance and regenerative capacity under systemic inflammatory conditions are not always sufficient to ensure effective tissue repair [80, 81]. In such cases, the use of cell-based products derived from healthy donors becomes necessary.

AD-MSCs, owing to their pronounced trophic and immunosuppressive properties, are widely applied in aesthetic medicine (anti-aging therapies), plastic and reconstructive surgery, as well as in the cell therapy of numerous diseases, including arthritis, osteochondrosis, multiple sclerosis, post-stroke conditions, and spinal cord injury. Notably, they have also been used in pathologies associated with local or systemic inflammation, such as cellulite, acute respiratory distress syndrome (ARDS), Crohn's disease, and osteoarthritis.

It can therefore be hypothesized that AD-MSCs obtained from healthy donors may also be used to correct adipose tissue dysfunction in patients with metabolic disorders. Although standard treatment of adipose tissue dysfunction primarily focuses on lifestyle modification (dietary interventions and physical activity) combined with pharmacological therapy, cell-based approaches are considered a promising strategy for restoring adipose tissue function and mitigating the deleterious consequences of its chronic inflammation [82].

Under conditions of systemic inflammation, transplanted MSCs are capable of homing to sites of tissue injury and contributing to the restoration of local and systemic homeostasis through anti-inflammatory, immunomodulatory, and regenerative mechanisms. Through the secretion of anti-inflammatory cytokines – including IL-10, IL-4, prostaglandin E2 (PGE2), transforming growth factor- β (TGF- β) – as well as chemokines (CCL2 and CCL5), and via direct interactions with immune cells mediated by PD-L1, PD-L2, CD54/ICAM-1, and CD106/VCAM-1, MSCs suppress immune cell proliferation and activation, resulting in reduced release of pro-inflammatory mediators [83, 84].

Although current therapeutic approaches for patients with SIRS have achieved partial success, there remains a need for the development of novel strategies, including cell-based therapies. In this context, mesenchymal stromal cells represent a particularly attractive therapeutic tool for inclusion in comprehensive treatment regimens for SIRS [85]. Preclinical studies have demonstrated the therapeutic efficacy of adipose-derived MSCs, showing their ability to attenuate pathological changes associated with metabolic syndrome, primarily through improvements in insulin resistance and regulation of glycolipid metabolism, as well as their capacity to suppress inflammation during the progression of SIRS [86].

Furthermore, the therapeutic potential of human AD-MSCs has been demonstrated in suppressing uncontrolled neutrophil activation and reducing tissue damage in a model of immune complex-mediated vasculitis. MSC-mediated inhibition of neutrophils was achieved through intercellular adhesion molecule 1 (ICAM-1)-dependent uptake and clearance of apoptotic neutrophils, resulting in a reduction of total neutrophil numbers.

In addition, MSCs increased the expression of extracellular superoxide dismutase 3 (SOD3), thereby decreasing superoxide anion concentrations and preventing neutrophil death, formation of neutrophil extracellular traps (NETs), and release of tissue-destructive neutrophil elastase, gelatinase, and myeloperoxidase. MSCs with suppressed SOD3 expression failed to exert protective effects. Collectively, these findings highlight the substantial therapeutic potential of MSCs in counteracting tissue damage under conditions of uncontrolled neutrophil activation [87].

Animal studies have demonstrated that MSC therapy leads to a significant reduction in body weight in obese mice. MSCs enhance lipolysis and suppress lipogenesis through increased activation of hormone-sensitive lipase (HSL) mediated by adenosine 5'-monophosphate-activated protein kinase (AMPK). In addition, MSCs promote mitochondrial biogenesis, thereby increasing energy expenditure and reducing adipocyte hypertrophy in adipose tissue [88]. MSCs also facilitate the clearance and restoration of damaged mitochondria via autophagy, thereby protecting pancreatic islet β -cells from cell death [89].

MSC transplantation has been shown to significantly reduce fasting blood glucose levels and insulin resistance in obese mice, which in turn may attenuate systemic inflammation. In a chronic inflammatory microenvironment, MSCs exhibit an immunosuppressive phenotype and exert anti-inflammatory effects through both direct cell–cell contact and paracrine signaling, with the latter representing the predominant mechanism of action [90].

The expression of insulin receptors was increased in skeletal muscle, adipose tissue, and liver of obese mice treated with AD-MSCs [91]. Other studies have reported that MSC therapy enhances the expression of insulin receptor substrate-1 (IRS-1) and glucose transporter type 4 (GLUT4) in skeletal muscle and adipose tissue of obese rats, thereby improving glucose uptake via activation of the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway [92, 93].

Levels of pro-inflammatory cytokines, including TNF- α , IL-6, and IL-1 β , were significantly reduced in rats with type 2 diabetes mellitus following administration of human MSCs [94, 95]. Other studies have demonstrated that injection of human AD-MSCs led to decreased expression of genes encoding pro-inflammatory cytokines (TNF- α , IL-6, and IL-1 β) and increased numbers of M2 macrophages in the adipose tissue of obese mice. Furthermore, human AD-MSC treatment significantly reduced adipose tissue mass, adipocyte size, and total fat mass, while also exerting a beneficial effect on the serum lipid profile in obese mice [96, 97]. In contrast, a study by Domingues C. et al. reported no significant changes in body weight in a mouse model of diabetes and obesity following AD-MSC therapy; however, a marked reduction in hepatic lipid and triglyceride content was observed based on histological analysis [98].

MSCs also exhibit antibacterial properties through the secretion of antimicrobial peptides such as β -defensin-2, lipocalin-2, LL-37, and hepcidin, which may contribute to the suppression of pathogen-associated molecular pattern (PAMP) levels under conditions of SIRS [99, 100].

In addition, the capacity of AD-MSCs to differentiate into insulin-producing cells has been established [101]. Li et al. confirmed that AD-MSCs can differentiate into insulin-producing cells through exogenous expression of pancreatic and duodenal homeobox 1 (Pdx-1) [102]. AD-MSCs derived from subcutaneous adipose tissue and cultured under specific conditions began to express genes essential for pancreatic development, including Pdx-1, Pax-6, and Isl-1. These transcription factors are critical for the reprogramming of non-pancreatic cells into fully functional β -cells, in which glucose stimulation induces the secretion of insulin and C-peptide [103]. Moreover, Karaoz et al. demonstrated that the differentiation potential of AD-MSCs into insulin-producing pancreatic cells was higher than that of bone marrow-derived MSCs (BM-MSCs). Thus, AD-MSCs may be considered a more favorable cell source than BM-MSCs due to their superior capacity to ameliorate metabolic complications of diabetes [104].

The ability of AD-MSCs to generate insulin-producing cells is of particular importance, as restoration and expansion of the pancreatic β -cell pool may directly influence key mechanisms underlying metabolic disorders – most notably insulin resistance – thereby contributing to the normalization of hyperglycemia and reduction of body weight.

However, the clinical application of MSCs for the treatment of inflammation-associated conditions, including metabolic syndrome, faces several challenges related to the selection of an optimal stem cell source, determination of an adequate therapeutic dose, and identification of the appropriate frequency of administration to maximize efficacy and safety [105]. Further studies are required to define the most suitable therapeutic strategies for specific diseases and to elucidate how SIRS influences the functional properties of MSCs.

In particular, the use of autologous AD-MSCs has been associated with variability in clinical outcomes, as cell characteristics may differ between patients not only due to biological factors such as age, sex, and body mass index, but also because of comorbid conditions and culture-related variables [106]. MSC donors may present with concomitant diseases (e.g., diabetes, obesity, renal insufficiency) or other risk factors. Consequently, their MSCs may exhibit dysfunction, features of senescence and apoptosis, impaired multilineage differentiation capacity, increased expression of pro-inflammatory factors, inadequate modulation of glycolipid metabolism, and disrupted energy homeostasis, all of which ultimately limit their therapeutic potential [107, 108].

CONCLUSION

Thus, adipose tissue is not merely an energy depot but also an active endocrine-immune organ that plays a key role in the development of chronic low-grade inflammation, metabolic syndrome, and systemic homeostatic disturbances. Under conditions of acute and chronic inflammation, adipocytes and adipose tissue-derived mesenchymal stromal cells undergo profound morphofunctional changes, accompanied by dysregulated adipokine secretion, reduced insulin sensitivity, activation of innate immunity, and impaired tissue regenerative potential.

Metabolic disorders, particularly obesity and type 2 diabetes, negatively affect the stem cell properties of AD-MSCs, reducing their proliferative activity, multipotency, anti-inflammatory and immunomodulatory potential, and shifting their secretory profile toward a pro-inflammatory phenotype. Therefore, donor selection is a critical factor for ensuring the effectiveness of cell therapy. Optimal MSC donors should be healthy individuals without chronic comorbidities (obesity, diabetes, metabolic syndrome, or other risk factors), as these conditions substantially limit the therapeutic potential of the cells.

MSC-based therapy, particularly using AD-MSCs, is considered a promising approach for correcting adipose tissue dysfunction and related metabolic and inflammatory disturbances. Their capacity for immunomodulation, suppression of chronic inflammation, improvement of insulin signaling, regulation of glycolipid metabolism, and stimulation of tissue repair offers new opportunities for treating metabolic syndrome and SIRS-associated conditions.

At the same time, clinical implementation of MSC therapy requires further basic and translational research aimed at elucidating the cellular mechanisms in an inflammatory microenvironment, standardizing cell sources and characteristics, optimizing doses, routes, and frequency of administration, and comprehensively assessing long-term safety and efficacy. Particular attention should be given to comparative analyses of autologous and allogeneic MSCs, as well as exploration of cell-free approaches, including the use of extracellular vesicles, as alternative or complementary therapeutic strategies.

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The authors declare that there is no potential conflict of interest regarding the research, authorship and/or publication of this article.

УДК 616-008.9:612.397:576.32/.36

Дисфункція жирової тканини в умовах запалення та перспективи її корекції за допомогою клітинної терапії

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РЕЗЮМЕ

Дисфункція жирової тканини в умовах запалення є важливим патогенетичним чинником розвитку метаболічних і системних захворювань, зокрема синдрому системної запальної відповіді та хронічних запальних процесів. У цьому огляді проаналізовано сучасні клінічні й експериментальні дані щодо функціональних, морфологічних та молекулярних змін жирової тканини за умов гострого та хронічного запалення.

Наведені дані свідчать, що в умовах запалення відбувається порушення секреторної активності адипоцитів і мезенхімальних стромальних клітин (МСК) жирової тканини, що проявляється підвищеною продукцією прозапальних цитокінів, хемокінів та інших медіаторів запалення. Прозапальне мікрооточення негативно впливає на біологічні властивості МСК, зумовлюючи зниження їх проліферативної та диференційної здатності, порушення регенеративного потенціалу, а також скорочення довжини теломер, що асоціюється з клітинним старінням. Також обговорюється роль імунних клітин жирової тканини, зокрема макрофагів, у підтриманні хронічного запалення та формуванні її дисфункції.

Окрему увагу в огляді приділено сучасним підходам до корекції асоційованих із запаленням змін жирової тканини з використанням клітинної терапії. Результати досліджень свідчать, що застосування МСК завдяки їхнім імуномодуючим, протизапальним та регенеративним властивостям є перспективною стратегією для відновлення гомеостазу жирової тканини та зменшення системного запалення.

ВИСНОВКИ. Отже, за умов гострого та хронічного запалення відбуваються суттєві зміни у функціонуванні адипоцитів і мезенхімальних стовбурових клітин жирової тканини, що призводить до порушення їхніх регуляторних і відновлювальних властивостей. Клітинна терапія на основі МСК може розглядатися як потенційний терапевтичний підхід для корекції дисфункції жирової тканини в умовах запалення, однак подальші дослідження мають бути спрямовані на уточнення механізмів дії стовбурових клітин, оптимізацію протоколів застосування та оцінку довгострокової безпеки й ефективності.

КЛЮЧОВІ СЛОВА: синдром системної запальної відповіді; хронічне запалення; жирова тканина; мезенхімальні стромальні клітини; імуномодуляція; клітинна терапія