Adipose Tissue Dysfunction: Impact on Metabolic Changes?

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ABSTRACT

Adipose tissue is a metabolically dynamic organ that is the primary site of storage for excess energy, but it serves as an endocrine organ capable of synthesizing a number of biologically active compounds that regulate metabolic homeostasis. However, when the capacity of expansion of this tissue exceeds, dysfunction occurs, favoring ectopic accumulation of fat in the visceral, which has been implicated in several disease states, most notably obesity. This review highlights the mechanisms involved in the structure of adipose tissue, tissue expandability, adipocyte dysfunction, as well as the impact of these events on the manifestation of important metabolic disorders associated with adipose tissue dysfunction. A literature search using Pubmed, Web of Science, Scopus, and Cochrane databases were used to identify relevant studies, using clinical trials, experimental studies in animals and humans, case-control studies, case series, letters to the editor, and review articles published in English, without restrictions on year of publication. The excessive ectopic lipid accumulation leads to local inflammation and insulin resistance. Indeed, overnutrition triggers uncontrolled inflammatory responses white adipose tissue, leading to chronic low-grade inflammation, therefore fostering the progression of important metabolic disorders. Thus, it is essential to advance the understanding of the molecular mechanisms involved in adipose tissue dysfunction in order to mitigate the negative metabolic consequences of obesity.

Introduction

Adipose tissue is an organ that performs a lot of significant physiological functions, which is why excess of adipose tissue in the body results in pathological states in many of its organs and systems [1]. Adipose tissue is not only a tissue, which stores fat and plays a protective role, it is also an important endocrine organ where signals sent from different tissues are generated and integrated. Adipose tissue is both morphologically and physiologically differentiated [2].

Adipose tissue consists of three types of adipocytes: white, brown, and beige, which have markedly different functions [3]. White adipose tissue (WAT) is the body's main energy reservoir, providing substrates for other tissues, such as muscle and liver [2]. Brown adipose tissue (BAT), on the other hand, specializes in heat generation by mechanisms associated with the oxidation of fatty acids, mainly through specific mitochondrial decoupling protein (UCP1), which dissipates the proton gradient along the inner mitochondrial membrane [1].

The beige adipocytes (also called inducible brown adipocytes, brown-in-white, or brite adipocytes) appear to differ from brown adipocytes not only in their respective location in WAT versus BAT depots, but also in their developmental program, and their responsiveness to adrenergic signaling with respect to mitochondrial regulation and UCP1 expression [3, 4].

Associated with this, we highlight the compartmentalization of adipose tissue in subcutaneous and visceral [5]. Subcutaneous fat is located beneath the skin and typically represents 80 % or more of total fat mass in humans, concentrated in the abdominal and gluteofemoral depots [4, 5]. In visceral adipose tissue, fat is located in the peritoneal cavity, corresponding to the omental and mesenteric depots [3]. WAT is an essential endocrine organ, secreting numerous hormones and other factors, collectively termed adipokines. Adipokines play major roles in regulating whole-body metabolism, including promoting insulin sensitivity (e. g., adiponec-

tin), insulin resistance (e. g., resistin, RBP4, lipocalin), and inflammation (e. g., TNF-a, IL-6, IL-1b, IL-8, IL-18, and sFRP5) [6].

An important aspect is the fact that the physiological expansion of subcutaneous adipose tissue, in particular, constitutes a safe storage place for excess lipids, a factor that contributes to the protection of the individual against lipotoxicity, with reduction of ectopic fat accumulation, mainly in the liver and skeletal muscle [7]. However, when the capacity of expansion of this tissue is exceeded, dysfunction occurs and does not expand properly to store the energy excess. This induces ectopic fat deposition in other tissues that regulates glucose homeostasis, an event commonly defined as "lipotoxicity". This mechanism leads to systemic insulin resistance and an increased risk of type 2 diabetes [8–10]. Numerous deleterious effects have been associated with the unhealthy expansion of the WAT, including inflammation, fibrosis, hypoxia, altered adipokines secretion, and mitochondrial dysfunction [4, 5].

Therefore, the objective of this review is to bring knowledge on mechanisms involved in the structure of adipose tissue, tissue expandability, adipocyte dysfunction, as well as the impact of these events on the manifestation of important metabolic disorders associated with adipose tissue dysfunction.

Literature search

A literature search using Pubmed, Web of Science, Scopus, and Cochrane databases were used to identify relevant studies, using clinical trials, experimental studies in animals and humans, case-control studies, case series, letters to the editor , and review articles published in English, without restrictions on year of publication. The following keywords, alone or in conjunction, were used to find relevant articles: "adipose tissue", "adipose tissue dysfunction", "white adipose tissue", "brown adipose tissue", "adipocytes", "adipogenesis", "lipolysis", "lipogenesis", "metabolic dysfunction" and "obesity". All eligible studies were in English. For this review, the inclusion criteria focused on structure and remodeling of adipose tissue, adipose tissue dysfunction and metabolic implications and main metabolic disorders arising from adipose tissue dysfunction.

Structure and remodeling of adipose tissue

The adipose tissue is a specialized connective tissue, formed by adipocytes, surrounded by a basal lamina and reticular fibers and constitutes the largest reserve of energy of the human body. The excess energy is stored in the form of triglyclycerides, and its efficiency is due to the ability to be stored in large quantities, dispensing with the presence of water as a solvent [11, 12].

The WAT presents large and spherical cells, which are formed by a single drop of fat that forms after the fusion of numerous smaller droplets and presents septa of connective tissue containing vessels and nerves [13]. BAT, on the other hand, has its staining determined by the large amount of mitochondria and blood vessels, as well as having smaller cells than unilocular ones and presenting a polygonal shape and numerous droplets of fat in its cytoplasm. This tissue has a reduced amount in adults, being more present in fetuses and newborns due to its specialty in heat production, a process stimulated by the action of norepinephrine [14].

Recent studies have shown that in addition to white and brown adipocytes, there is also beige adipocyte, which does not present the same embryonic expression profile in all white fat deposits [1, 4, 15]. These differences are important because beige adipocytes may present different origins and characteristics of other tissues, such as the amount of nerve fibers, vascularization and environmental exposure conditions. It is noteworthy that subcutaneous fat presents expressive amounts of beige cells, occurring mainly by cold stimulation and β3-adrenergic receptors [16].

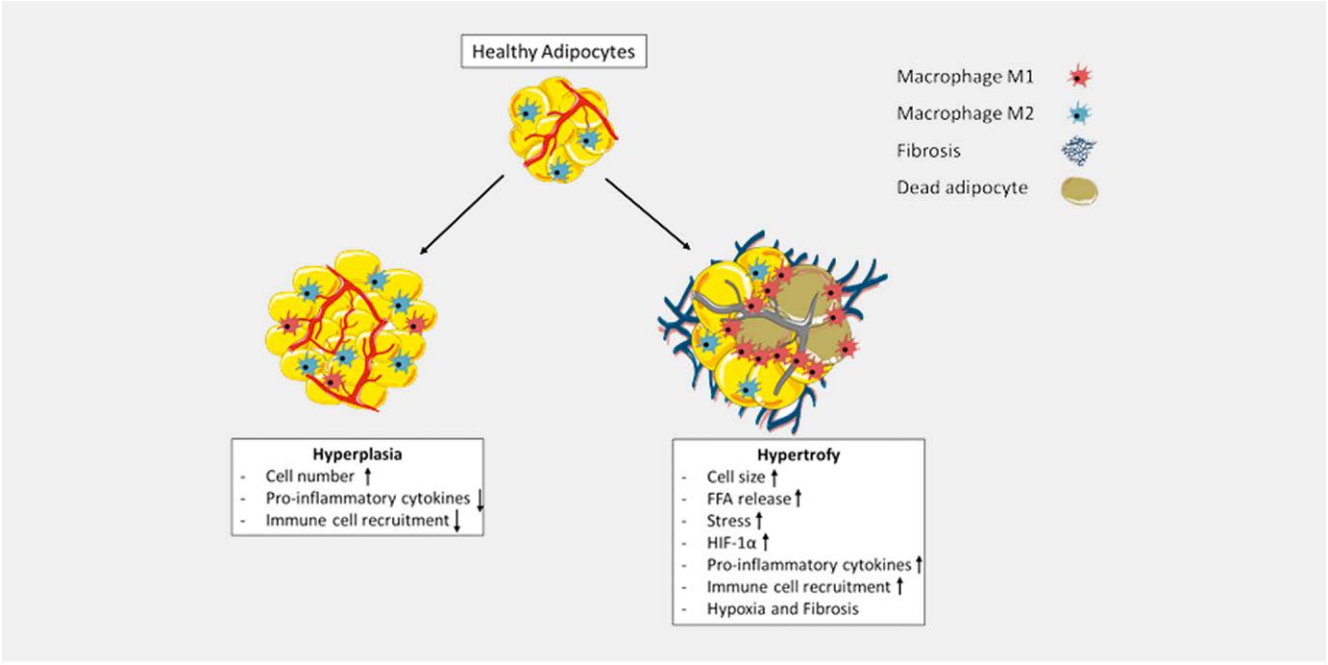
Fat cells develop derived from cells called pre-adipocytes, which are associated with blood vessels and derived from endothelial cells of adipose tissue (▶ **Fig. 1**). During embryonic development, the vascular network develops before the adipocytes and the extracellular matrix that supports the blood vessels is the first to be deposited, showing a crucial role of the vascular system in the development of adipose tissue. Thus, at this stage of development there is a close communication between stroma-vascular fraction and adipocytes, which results in a mutual control between angiogenesis and adipogenesis [17].

Pre-adipocytes are multipotent cells, capable of differentiating into macrophages, muscle or bone progenitors, brown fat, and other cell types. Pre-adipocytes generate adipokines, paracrine factors, hormones and metabolic signals differently from mature adipose cells [18]. In addition, they exhibit robust innate immune responses to bacterial antigens, recruit macrophages and other immune effectors, as well as participate in the process of regulating the immunological activity of adipose tissue [19]. Thus, the gene expression profiles of these cells are closer to those of macrophages than to those of the fat cells themselves [20].

Pre-adipocytes differ in fat cells in response to insulin-like growth factor 1 (IGF-1), lipids, glucocorticoids, and other signs. IGF-1, for example, is probably the main promoter of adipogenesis, and not insulin itself, as insulin receptors are not expressed in high amounts until the pre-adipocytes become mature adipose cells [17].

There are at least two pre-adipocyte subtypes identified in adipose tissue, the first with the highest response to replication, differentiation, and expression of adipogenic transcription factors and lower apoptosis in response to tumor necrosis factor α (TNF-α). The second is a subtype resistant to adipogenesis, ensuring that not all pre-adipocytes become adipose cells under favorable conditions. Such subtypes may facilitate tissue plasticity, for example by differentiating into fat cells with distinct properties, or by selecting for the apoptosis-resistant subtype [21]. It is noteworthy that adipocytes have different characteristics in the various stages of development, and in adulthood, there is a well-developed vascular network, where each adipocyte is surrounded by at least one capillary, fenestrated and rich in transendothelial channels, which allow communication with adipocytes. This vascular network is dynamic and continuously adapted to the changes in nutritional flows, which influences the behavior of adipocytes during WAT expansion [22].

About the expansion of subcutaneous adipose tissue, this is determined by the formation of new adipocytes and by the growth capacity from those already formed. New adipocytes develop from their precursors, known as pre-adipocytes, vascular stroma, as well as adipose or mesenchymal stem cells. The expansion of this tissue is regulated by the expression of genes, proteins and metabolites of different cell types, and depends mainly on the total number of stem cells available to differentiate into new adipocytes [3, 23].



▶ **Fig. 1** White adipose tissue dysfunction: Hypertrophic expansion through increased adipocyte size is associated with harmful phenomena such as increased release of basal fatty acids, release of pro-inflammatory cytokines, recruitment of immune cells, hypoxia, fibrosis, decreased adiponectin, and impaired insulin sensitivity.

Adipocyte hypertrophy is usually associated with abnormal capillary formation, while hyperplasia is associated with increased angiogenesis and the development of new capillaries, the latter being the least harmful form of adipose tissue expansion, given the formation of small, well-irrigated adipocytes with less inflammatory activity than hypertrophic ones [24].

In order to store excess energy, the adipose tissue undergoes remodeling processes, among them: (1) Higher nutrient flux [1]; (2) Tissue expansion through coordination of hypertrophy and/or hyperplasia [2]; (3) Microvascular compression by the adipocytes' hypertrophy [2]; (4) Reduction of O_2 saturation on the cells [5]; (5) Increase mitochondrial dysfunction and Reactive Oxygen Species (ROS) generation on mitochondria [1] (6) Impairment on Redox homeostasis, increasing ROS production [1]; (7) Pro-oxidative environment and with endoplasmic reticulum (ER) stress [25]; (8) ER stress and mitochondrial dysfunction [25]; (09) Oxidative Stress [3]; (10) increase the macrophage migration and polarization to a pro-inflammatory phenotype, and (11) Remodeling of the vasculature and extracellular matrix [25].

It is worth mentioning that during the process of expansion of adipose tissue, local hypoxia phenomena may occur, which increases the expression of angiogenic, cytokine and adipokine factors. The balance between these factors determines the density and permeability of the vessel and, therefore, the physiological or pathophysiological expansion of the adipose tissue [26].

That being the case, angiogenesis is a physiological process through which new blood vessels form from preexisting vessels, being important for the maintenance of adequate tissue remodeling and expansion [27]. In WAT remodeling, the angiogenesis frequently precedes adipogenesis, however, in an inefficiency situation, such process seems to play an important role in adipose tissue dysfunction [28, 29].

It is appropriate to mention the important role of the extracellular matrix in the tissue expansion process of adipose tissue as it deals with a complex structure composed of different proteins, proteoglycans and polysaccharides and is involved in the modulation of biological processes such as cell adhesion, migration, repair, survival and development. In adipose tissue, in particular, the extracellular matrix is composed mainly of collagen types I, II, III and IV, fibronectin and laminin, besides allowing the formation of new blood vessels, essential process in the expansion of healthy adipose tissue [30].

The adipose tissue expansion depends on extracellular matrix remodeling through hydrolysis/collagen redeposition cycles. However, when its expansion occurs in a dysfunctional way, excessive and unregulated accumulation of collagen and other extracellular matrix components occurs, resulting in fibrosis, which limits the adipocyte expansion capacity [31].

Metabolic and endocrine functions of the adipose tissue

Regarding the metabolic functions of WA, it must be noted that in a situation of positive energy balance, this tissue has the function of storing energy in the form of lipids, mainly in intracellular triacylglycerol droplets [32]. These droplets are coated by a group of proteins, the main one being Perilipin A (PLIN A), which prevents the contact of the triacylglycerols stored with the cytoplasm [33, 34].

However, in a negative energy balance situation, lipolysis occurs, a process characterized by the hydrolysis of triacylglycerols

in free fatty acids and glycerol, which in turn, are released into the bloodstream and later used by other tissues [35]. In this way, adipose tissue is able to recognize the metabolic state of the organism, not only by local energy sensors, but also by means of different signaling pathways, mainly of the intestine [11]. In addition, adipose tissue has other functions such as thermal insulation, action in inflammatory processes, besides playing an important role in glucose homeostasis and endocrine function, such as leptin release [12].

The main metabolic actions of WAT are classified into lipogenic and lipolytic activities. Lipogenic activity involves all metabolic processes that result in biosynthesis, incorporation and storage of triacylglycerols in the intracytoplasmic fat droplet. While the lipolytic activity concerns the hydrolysis of the stored TAG and the release of free fatty acids (FFA) and glycerol [36].

For the lipogenesis process, there is a need for a glycerol 3-phosphate and FFA source complexed with coenzyme A (CoA), making up acetyl-CoA, derived from glycolytic pathway and biosynthesis from acetyl-CoA or FFL uptake, respectively. Once in the cytosol, the FFL binds to fatty *acid-binding proteins* (FABP), which transports it to coenzyme A. This process is performed by another integral membrane protein, acyl-CoA synthase (ACS). At the end of this stage, acyl-CoA is taken by another protein, the acyl-CoA-binding protein, to the glycerol 3-P esterification sites, finalizing the synthesis of TAG, which are transferred to the cytoplasmic fat droplet [14].

About the lipolytic action, this is characterized by the hydrolysis of the stored triacylglycerol and consequent release of fatty acids and glycerol into the bloodstream. This process is dependent on the activation of the enzyme lipase hormone sensitive and stimulated by catecholamines, particularly in fasting situation, high energy demand, such as physical exercise, or under stress conditions. Thus, these catecholamines interact with β3-adrenergic receptors, increasing free fatty acids in the bloodstream [37].

Regarding the endocrine function of adipose tissue, it is emphasized that this plays a central role in the control of metabolism and interacts with different organs and systems, through substances and hormones that act stimulating actions such as Adipogenesis, substrate secretion and metabolization site of steroid molecules [38].

Another aspect that has been extensively investigated among the actions of adipose tissue, deals with its role in antimicrobial defense, wound healing and inflammation [39]. In this sense, we highlight the immune cells presented in adipose tissue include macrophages, neutrophils, dendritic cells, eosinophils, *natural killer* cells (NK) and innate lymphoid cells, as well as adaptive immunity cells such as B and T cells (CD4 and CD8 and regulatory cells T (TREG) [40, 41].

Macrophages are the most widely studied myeloid cells present in adipose tissue, and currently two phenotypes with distinct functions have been identified: classically activated macrophages (M1) and alternatively activated macrophages (M2). The M1 phenotype differs under the influence of pro-inflammatory cytokines and acts in the beginning and maintenance of inflammation by producing reactive oxygen and nitrogen species, nitric oxide synthase and pro-inflammatory cytokines such as TNF-α, interleukin 1β (IL-1β) and interleukin 6 (IL-6) [42–44]. The M2 phenotype, induced by anti-inflammatory cytokines such as IL-4, IL-10 and IL-13, act in the resolution of inflammation and tissue regeneration [45–47].

In this sense, adipose tissue synthesizes and releases several adipokines, including interleukin-6 (IL-6), transforming growth factor-β (TGF-β), adipsins, angiotensinogen, plasminogen activator inhibitor-1 (PAI-1), adiponectin, resistin, visfatin, leptin, and vascular endothelial growth factor (VEGF) [48]. These substances perform relevant physiological functions, such as the regulation of immune response, blood pressure control and glycemic homeostasis [49, 50].

Adipose tissue dysfunction and metabolic implications

Adipose tissue has a safe threshold of expansion for fat storage, without development of dysfunction. However, in a situation of prolonged positive energy balance, the limit of expansion of adipocytes of subcutaneous adipose tissue is reached. From then on, lipids are stored in the visceral compartment and ectopic form in several organs in the body, mainly in the liver, heart, kidney, pancreas and muscles [51].

In this perspective, it should be considered that the absolute fat mass is not the determining factor for the development of metabolic disorders in obese individuals, but rather the inability of the white adipose tissue to expand and adequately accommodate the energy surplus, since the hyperplasia process is limited and hypertrophy does not meet the high energy demand [52, 53]. One of the mechanisms that explains the association between adipocyte hypertrophy and the manifestation of metabolic disorders, involves alterations in the process of angiogenesis, because the vascularization of these cells does not follow proportionally the increase in their size, which results in inadequate supply of oxygen and nutrients, favoring tissue dysfunction [24].

The hypoxia in adipose tissue during its initial expansion induces stress signaling, which in turn facilitates angiogenesis through positive regulation of a number of genes, including Vascular Endothelial Growth Factor A (VEGF) [54]. However, continuous signaling via stress resulting from hypoxia reduces VEGF signaling, resulting in impairment of angiogenesis, which contributes to increased macrophage infiltration and chronic inflammation [55].

Associated with this, the limited oxygen supply and excessive deposition of extracellular matrix components, such as collagen and osteopontin, also trigger adipocyte necrosis and low-grade chronic inflammation, being the latter characterized predominantly by infiltration of pro-inflammatory macrophages [56, 57]. Hypoxia also promotes positive regulation of hypoxia-inducible factor 1α (HIF-1α), favoring adipose tissue fibrosis. It is worth mentioning that HIF-1α is overexpressed in the adipose tissue of obese people and stimulates the attraction and retention of macrophages in adipocytes. Thus, in addition to contributing to physical restriction to adipose tissue expansion, excess deposition of the extracellular matrix can contribute to adipocyte death, tissue inflammation and metabolic dysfunction (▶ **Fig. 1**) [58, 59].

A study on the subject found a lower amount of fibrosis in the visceral adipose tissue of diabetic individuals [60]. Similarly, Lackey et al. (2014) [60] found lower collagen content in the visceral adipose tissue of metabolically unhealthy obese patients when compared to metabolically healthy obese patients. Thus, fibrosis

reduction seems to be associated with increased adipocyte hypertrophy, reduced preadipocyte hyperplasia, evidencing the role of extracellular matrix remodeling and fibrosis in tissue dysfunction [54].

These events induce macrophage infiltration into obese adipose tissue through increased expression of both leptin and macrophage migration inhibition factor, which inhibits tissue macrophage emigration [61, 62]. In addition, the supernutrition present in obesity stimulates the secretion of chemokines by adipocytes, such as the monocyte chemoattractant protein-1 (MCP-1), attracting monocytes to adipose tissue, which later differentiate into macrophages [63].

The infiltration of macrophages in adipose tissue and the pro-inflammatory microenvironment installed in obesity leads to the alteration of the phenotype of these cells to type M1. These, in turn, accumulate around the hypoxic regions, forming "Crown-like Structures", producing pro-inflammatory cytokines, such as IL-6 and TNFα, which have a great impact on the insulin signaling cascade, in addition to contributing to local and systemic inflammation [38, 64].

It is important to point out that the polarization of macrophages to type M1 is also favored by the accumulation of lipids within these cells, since, in an attempt to reduce lipotoxicity, these cells phagocytize the triglyceride droplets, which results in the accumulation of lipids within macrophages, transforming them into foamy cells that, in turn, secrete pro-inflammatory cytokines, such as IL-6 [65].

The chemokines and cytokines produced in adipose tissue are key regulators not only in the recruitment of macrophages, but also of other immune cells. With regard to T-lymphocytes, studies show that the CD8 fraction increases with the progression of obesity, while the CD4 and TREG fractions decrease. In addition, CD8 cell infiltration precedes macrophage accumulation in adipose tissue, while immunological depletion of these cells reduces the infiltration of M1 macrophages and the expression of inflammatory cytokines, indicating that these cells may be involved in the beginning and maintenance of the inflammatory cascade in obesity [41, 66].

It is worth noting that the abnormal polarization of macrophages for type M1 mediates metabolic changes in this tissue, and some studies indicate that the degree of visceral adiposity and the frequency of infiltrated macrophages in obese adipose tissue correlate significantly with the progress of atherosclerosis, insulin resistance and low-grade chronic inflammation [67, 68].

Neutrophils are also cells that stand out for their recruitment at places of acute inflammation in obese adipose tissue, being mediated by cytosolic phospholipase A2α. These cells, in turn, produce elastases, a substance that can induce insulin resistance by degrading the insulin receptor substrate 1 in adipocytes and hepatocytes [69, 70]. In addition, neutrophils also secrete myeloperoxidase, which contributes to systemic inflammation and tyrosine nitration, leading to a reduction in the levels of this protein and modification in the function of the insulin β receptor [71]. In this way, the recruitment of these cells contributes to the development of inflammation and insulin resistance in obese adipose tissue.

Differently, eosinophils are cells involved in the regulation of adipose tissue homeostasis, through the production of IL-4, a cytokine essential for the maintenance of M2 macrophages [39]. Recently, studies have shown that the number of eosinophils is linked to another population of immune cells called innate lymphoid cells (ILC). These cells, in turn, are categorized into three subtypes: (i) ILC1, which are activated by IL-12, IL-15 and IL-18 and secrete IFN-γ and TNF; (ii) ILC2, which are activated by IL-25 and IL-33 and express IL-4, IL-5 and IL-13, and (iii) ILC3 which are triggered by IL-1β and IL-23 and release IL-17 and IL-22 [72, 73].

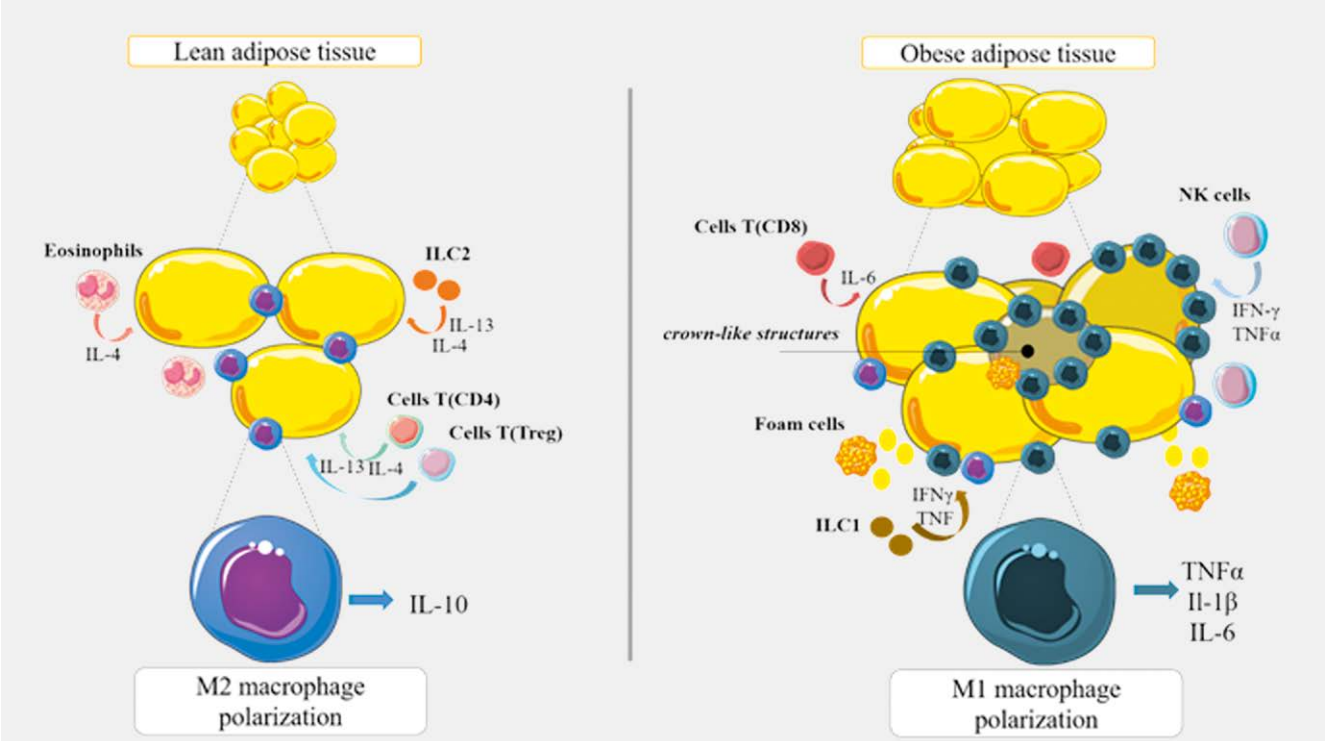
In this context, it was identified that the subtype ILC2 predominates in lean WAT and contributes to its homeostasis by maintaining the numbers of eosinophils and macrophages of type M2, since it secretes the cytokines IL-5 and IL-13. In obesity, the ILC1 subtype produces large amounts of Interferon-gamma (IFN-γ), thus contributing to the polarization of M1 macrophages and promoting obesity-related insulin resistance [74].

Similar to the ILC1 subtype, natural killer cells (NK), after activation by IL-12, IL-15 and IL-18, secrete cytokines and chemokines such as TNF, IFN-γ, GMCSF and CCL2 and promote the recruitment and activation of other immune cells at the place of inflammation. In this sense, several studies have observed an increase in the number of these cells in the adipose tissue and in the blood circulation of obese individuals or with type 2 diabetes mellitus, when compared to the control group, highlighting the harmful role of NK cells in obesity-related inflammation and metabolic dysregulation, as well as contributing to insulin resistance in obesity (▶ **Fig. 2**) [75, 76].

Systemic oxidative stress constitutes another disorder present in the dysfunctional expansion of adipose tissue, due to an imbalance between reactive oxygen species production and antioxidant capacity, leading to disruption of redox signaling and control and/or molecular damage [77]. This disturbance can be classified according to intensity, ranging from physiological oxidative stress (eustress) to toxic oxidative load (dysstress), which impairs redox signaling and promotes damage to biomolecules, with pathophysiological consequences [78]. About this disorder, several studies have already demonstrated that hypertrophy of adipocytes increases the secretion of pro-inflammatory cytokines and adipokines, the main contributing factor to the excessive production of reactive oxygen and nitrogen species nitrogen species in obese organisms [79, 80].

The accumulation of reactive species induces DNA damage, including point mutations and chromosomal aberrations, as well as activates signal translation pathways, altering the expression of several genes [78]. Chronicity of this process promotes peroxidation of membrane lipids and aggression to tissue proteins, contributing to the pathogenesis of several metabolic diseases [81].

When adipocytes reach their expansion limit due to increased fat deposition, it disrupts metabolic homeostasis causing adipose inflammation and alterations in autophagy and ER functions (induced ER stress) [82]. Several factors alter ER functions, leading to metabolic dysfunction within the cell. One of the mechanisms is through, over accretion of fat in adipocytes, which disrupts normal ER activities, such as protein folding/maturation and lipid homeostasis. This, in turn, stresses the ER and activates numerous adaptive responses including unfolded protein responses (UPRs), ER-associated protein degradation (ERAD) as well as autophagy to reinstate metabolic homeostasis [77, 83].



▶ **Fig. 2** Role of the immune system in lean versus obese adipose tissue: In lean adipose tissue, CD4-type helper T cells produce anti-inflammatory cytokines, such as interleukin (IL)-4 and 13, which promote macrophage polarization to type M2. M2 polarization is also induced by regulatory T cells (Tregs) and eosinophils via IL-4. M2 macrophages secrete other anti-inflammatory signals, such as IL-10, which maintain insulin sensitivity in lean adipose tissue. On the other hand, cytokines secreted by CD8-type T cells, such as IL-6, stimulate the polarization of M1-type macrophages in obese adipose tissue. Other immune cells are also higher in obese adipose tissue, which contribute to insulin resistance, including natural killer cells and ILC1. Furthermore, in obese adipose tissue, macrophages are not homogeneously distributed, but aggregated around dead adipocytes, forming crown-like structures. Foam cells are also present in order to phagocytose lipids from overloaded adipocytes. M1 macrophages are pro-inflammatory, secreting cytokines such as TNF-α and IL-1β, which perpetuates inflammation in obese adipose tissue and causes other metabolic disorders, such as insulin resistance.

The UPRs are primarily involved in maintaining metabolic stability by governing proper protein folding or degradation. Yet, continuous activation of UPRs in adipocytes is detrimental, coinciding with adipose dysfunction leading to obesity and its related comorbidities [77, 82]. Uncontrolled ER stress in adipose tissue indeed could alter cellular functions, including lipid and glucose metabolism, inflammation, insulin signaling, and autophagy, disturbing the metabolic equilibrium of adipocytes [83].

In this area, an important aspect that should be highlighted is the effect of interventions for weight loss, for example bariatric surgery and low-calorie diets in reducing the number of circulating immune cells in adipose tissue that implies the attenuation of local and systemic inflammation [84, 85].

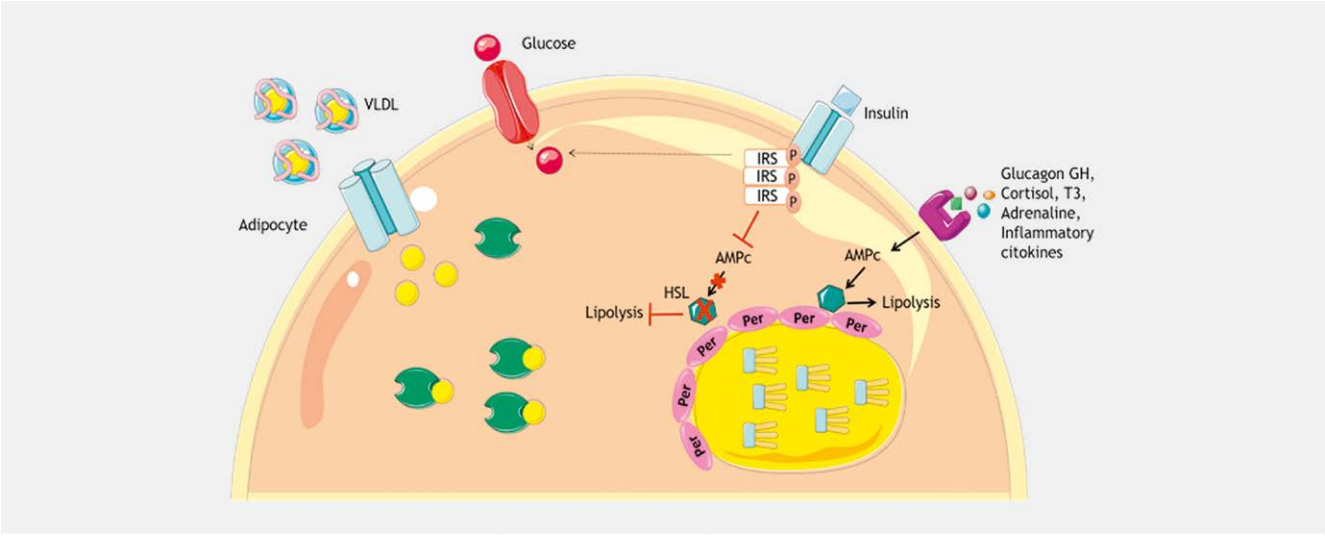
Insulin resistance and dyslipidemia

Regarding the impact of adipose tissue dysfunction on glycemic control and dyslipidemias, the influence of body fat distribution on changes in glucose metabolism and dyslipidemias stands out, large visceral fat cells are more strongly linked to disorders in lipid metabolism, while large subcutaneous adipose cells correlate with hyperinsulinemia and insulin resistance (▶ **Fig. 3**) [24, 86].

Regarding the contribution of adipose tissue dysfunction to insulin resistance, it is worth noting that, in situations where positive energy balance is associated with dysfunction of subcutaneous adipose tissue, there is an increase of basal lipolysis in hypertrophic adipocytes, favoring the release of non-esterified fatty acids (NEFA) into the bloodstream. This process triggers multiple inflammatory signaling pathways in macrophages and adipocytes, as NEFA may promote inflammation by binding to Toll-like 2 and 4 receptors through the Adaptive Protein Fetuin-A (FetA), which results in the activation of Nuclear Factor Kappa B (NF-κB) [87].

Inflammation favors the manifestation of insulin resistance via activation mechanisms of NF-κB transcription factor signaling. In this sense, adipose tissue dysfunction activates the IKK kinase complex, favoring proteasomal degradation of IκBα, which induces nuclear translocation of NF-κB, which consequently increases the expression of target genes of this transcription factor, such as IL-6, TNF-α, transforming growth factor beta (TGF-β) and receptor for advanced glycosylation end product, important molecules in the induction of insulin resistance (RAGE) [88, 89].

The ectopic fat deposition is also an important factor in reducing local and systemic insulin sensitivity, and the accumulation of



▶ **Fig. 3** Mechanisms of lipid storage in adipocytes and their mobilization from lipid droplets: Lipolysis is inhibited by insulin signaling and promoted by other hormones like glucagon, GH, cortisol, T3, or adrenaline, due to the stimulation of AMPc and HSL. cAMP: Cyclic adenosine monophosphate; FATP: Fatty acid binding protein; FFA: Free fatty acids; HSL: Hormone-sensitive lipase; IRS-1: Insulin receptor substract-1; LPL: Lipoprotein lipase; PerA: Perilipin A; VLDL: Very-low density lipoprotein.

diacylglycerides in hepatocytes activates protein kinase C (PKC), which reduces insulin-stimulated phosphorylation of IRS-2 and AKT serine/threonine kinase 2 (AKT2), as well as the ability to activate glycogen synthesis [90, 91]. Thus, the ectopic accumulation of fat in the liver results in a reduction of glucose uptake and increased production of this substrate, which consequently potentiates insulin resistance [88, 89].

The ectopic accumulation of diacylglycerols and ceramides in muscle tissue also activates PKC, favoring the phosphorylation of IRS1 in serine residues impairing the activation of PI3K, with consequent reduction of glucose transporter activity (GLUT4) and glucose uptake [88]. Ectopic lipid deposition in the heart results in a form of "cardiac lipotoxicity" characterized by cardiac insulin resistance, cardiac myocyte apoptosis and contractile dysfunction, for the reason that diacylglycerols can also activate various PKC isoforms, involved in the development of insulin resistance [89].

Regarding dyslipidemia associated with adipose tissue dysfunction, changes in the performance of important enzymes stand out, such as the increased activity of hormone-sensitive lipase, as well as the inhibition of lipoprotein lipase, which contributes to promoting the flow of free fatty acids to hepatocytes, which increases the synthesis of very-low-density lipoproteins (VLDL-c), and consequently hypertriglyceridemia [92].

The excess of triglycerides in the bloodstream induces a reduction in the activity of lecithin cholesterol acyl transferase, an important substrate in the synthesis of high-density lipoproteins (HDL-c) and phospholipid transport protein, being the latter responsible for the transfer of triglyceride-rich lipoprotein phospholipids to HDL-c. This metabolic dysfunction implies the impairment of the maturation of HDL-c lipoprotein and consequently its role in the reverse transport of cholesterol [90].

Associated with this, hypertriglyceridemia also accentuates the activity of cholesterol ester transfer protein, an enzyme that acts on the exchange of cholesterol esters and triglyceride between lipoproteins and, as a consequence, with formation of LDL-c and HDL-c particles with low cholesterol concentrations and rich in triglyceride [93, 94].

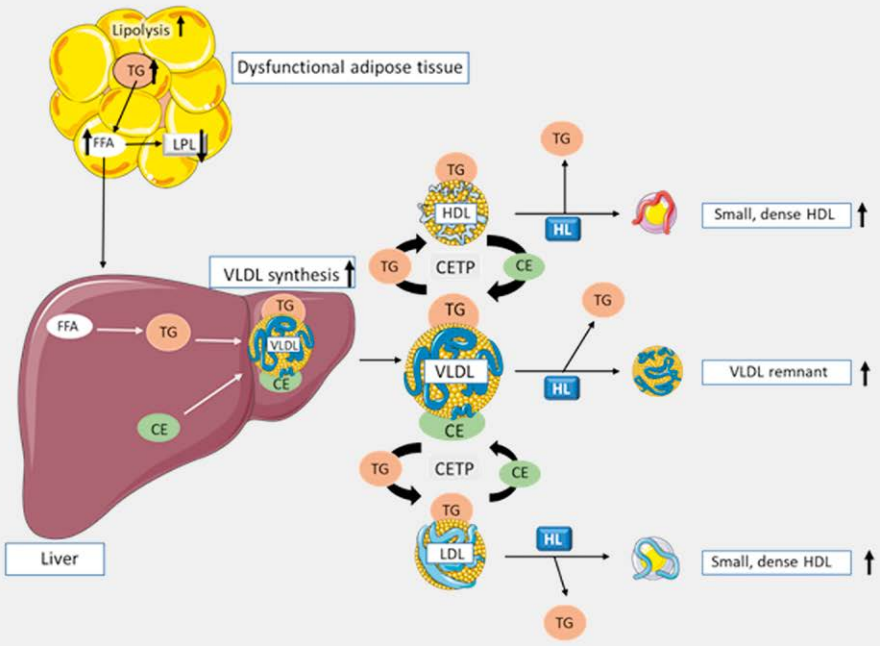
In this regard, it is worth noting that the high serum concentration of LDL-c and HDL-c particles rich in triglycerides stimulates the activity of the enzyme hepatic lipase to release apoprotein apoA-I from the HDL-c particle, forming remnants of HDL-c, these being possibly eliminated by bile, reducing their serum concentration. Thus, as a result of the reduced HDL-c values associated with the formation of small and dense LDL-c particles, there is a higher risk for the development of cardiovascular disease (▶ **Fig. 4**) [95].

In this scenario, based on the information obtained on the subject, it is verified that the literature clearly brings the various mechanisms involved in the dysfunction of adipose tissue, as well as its impact on the development of important disorders associated with obesity. Associated with this, it is highlighted that such dysfunction can be achieved in different degrees of adiposity and is not necessarily related to total adipose mass, which allows its classification into different phenotypes, such as metabolically healthy and unhealthy obesity.

Conclusions

The data presented in this review emphasize the function, growth, and expansion of human adipose tissue, along with the development of complications associated with dysfunction of this tissue, including inflammation, accumulation of ectopic fat, insulin resistance, and dyslipidemia.

The limited storage capacity of excess lipids in adipose tissue favors the development of metabolic disorders associated with obesity. Thus, it is essential to advance the understanding of the



▶ **Fig. 4** Development of dyslipidemia in obesity; Reference: Jung, Choi [95]. In dysfunctional adipose tissue there is an increase in lipolysis and, consequently, a higher concentration of triglycerides and free fatty acids, which contribute to a lower activity of lipoprotein lipase. There is then an increased release of free fatty acids from the adipose tissue to the liver, which leads to greater production of VLDL-c in this tissue, thus promoting hypertriglyceridemia. The triglyceride present in the VLDL-c structure is exchanged for low-density lipoprotein (LDL) cholesterol esters and high-density lipoprotein (HDL) cholesterol esters for the esterified cholesterol transport protein, producing triglyceride-rich LDL and HDL. Triglycerides in these lipoproteins are hydrolyzed by hepatic lipase, producing small, dense LDL and HDL. Decreased HDL concentration and the formation of small, dense LDL particles are associated with an increased risk of cardiovascular disease. EC: Cholesterol esters; CETP: Esterified cholesterol transport protein; FFA: Free fatty acids; HDL: High density lipoproteins; HL: Hepatic lipase; LDL: Low-density lipoproteins; LPL: Lipoprotein lipase; TG: Triglyceride; VLDL: Very low density lipoprotein. hepatic lipase.

molecular mechanisms involved in adipose tissue dysfunction in order to mitigate the negative metabolic consequences of obesity.

Conflict of Interest

The authors declare that they have no conflict of interest.

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