# Molecular and pathophysiological relationship between obesity and chronic inflammation in the manifestation of metabolic dysfunctions and their inflammation-mediating treatment options (Review)

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**Abstract.** Obesity reaches up to epidemic proportions globally and increases the risk for a wide spectrum of co-morbidities, including type-2 diabetes mellitus (T2DM), hypertension, dyslipidemia, cardiovascular diseases, non-alcoholic fatty liver disease, kidney diseases, respiratory disorders, sleep apnea, musculoskeletal disorders and osteoarthritis, subfertility, psychosocial problems and certain types of cancers. The underlying inflammatory mechanisms interconnecting obesity with metabolic dysfunction are not completely understood. Increased adiposity promotes pro-inflammatory polarization of macrophages toward the M1 phenotype, in adipose tissue (AT), with subsequent increased production of pro-inflammatory cytokines and adipokines, inducing therefore an overall, systemic, low-grade inflammation, which contributes to metabolic syndrome (MetS), insulin resistance (IR) and T2DM. Targeting inflammatory mediators could be alternative therapies to treat obesity, but their safety and efficacy remains to be studied further and confirmed in future clinical trials. The present review highlights the molecular and pathophysiological mechanisms by which the chronic low-grade inflammation in AT and the production of reactive oxygen species lead to MetS, IR and T2DM. In addition, focus is given on the role of anti-inflammatory agents, in the resolution of chronic inflammation, through the blockade of chemotactic factors, such as monocytes chemotractant protein-1, and/or the blockade of pro-inflammatory mediators, such as IL-1β, TNF-α, visfatin, and plasminogen activator inhibitor-1, and/or the increased synthesis of adipokines, such as adiponectin and apelin, in obesity-associated metabolic dysfunction.

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*Abbreviations:* AGEs, advanced glycation end products; AMPK, AMP-activated protein kinase; APJ, angiotensin II protein J; AT, adipose tissue; ATP, adenosine triphosphate; BMI, body mass index; CCR, C-C motif chemokine receptor; CRP, c-reactive protein; CVDs, cardiovascular diseases; eNOS, endothelial nitric oxide synthase; FADH2, flavin adenine dinucleotide (reduced form); FFAs, free fatty acids; FRs, free radicals; HDL, high-density lipoprotein; HIF-1α: hypoxia-inducible factor-1α; HMWA, high molecular weight adiponectin; IL-1Ra, interleukin-1 receptor antagonist; iNOS, inducible nitric oxide synthase; IR, insulin resistance; IRS-1, insulin receptor substrate 1; JAK, janus kinase; JNK, c-Jun N-terminal kinase; MAPK, Ras/Raf/mitogen-activated protein kinase; MetS, metabolic syndrome; MCP, monocytes chemoattractant protein; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NO, nitrogen oxide; NOD, non-obese diabetic; OS, oxidative stress; PAI-1, plasminogen activator inhibitor-1; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B; PPAR, peroxisome proliferation activating receptor; ROS, reactive oxygen species; STAT, subcutaneous adipose tissue; T2DM, type-2 diabetes mellitus; TGs, triglycerides; TZDs, thiazolidinediones; UCP1, uncoupling protein 1; VAT, visceral adipose tissue; VLDLs, very low density lipoproteins; VSMC, vascular smooth muscle cells; WAT, white adipose tissue

*Key words:* obesity, oxidative stress, inflammation, mediators, cytokines, adipokines, metabolic syndrome, insulin resistance, type-2 diabetes mellitus

## Contents

## 1. Introduction

Adipose tissue (AT) is the main energy store derived from food intake in the form of triglycerides (TGs) and controls lipid mobilization (1,2). Furthermore, AT is an active endocrine organ, since it synthesizes and secretes several hormones, cytokines and other bioactive factors, signaling to other metabolic organs, such as the liver, pancreas and brain modulating systemic metabolism, whilst also maintaining body temperature (1,2). AT contains multiple cell types, including adipocytes, adipocytes progenitors, endothelial cells, macrophages, fibroblasts and leucocytes (1-3). Adipocytes, also called adipose cells or fat cells, are the predominant cell type in AT. There are three types of adipocytes including white, brown and beige (brite). They differ in structure, location, abundance of mitochondria, thermogenic gene expression and function (2,4). White adipocytes are unilocular with a low number of mitochondria and low oxidative rate (2). The cells have a high capacity of energy storage in the form of TGs. In addition, white adipocytes can prevent ectopic lipid deposition and therefore protect organs such as skeletal muscle and the liver from lipotoxicity (2). Brown adipocytes are specialized cells with multilocular lipid droplets, high numbers of mitochondria and enrichment of uncoupling protein 1 (UCP1), a high oxidative capacity and actively participate in energy consumption via thermogenesis (2). In newborn humans, brown AT plays an important role in thermogenesis mediated by the expression of UCP1 (5). In adult humans, it has been found that the amount of brown AT is inversely associated to body mass index (BMI), especially in older individuals indicating the importance of brown AT in energy metabolism (5). Beige adipocytes are a distinct type of adipocyte with multilocular morphology within white AT (WAT) and extremely low UCP1 expression and are capable of thermogenesis (2). Beige adipocytes exist mainly in subcutaneous white fat, but a small portion in visceral fat can be found as well. Acute cold exposure markedly triggers the recruitment and activation of beige adipocytes (2). Based on its location in the body, WAT can be further divided into two types of specific regional depots, the subcutaneous depots and the visceral depots (6). Subcutaneous fat is located under the skin in areas such as the abdomen, thighs, hips and buttocks, however, visceral fat surrounds the intrathoraci organs, the intraperitoneal organs, such as the greater and lesser omentum, mesentery, mesocolon and peritoneum, and the retroperitoneal organs, such as the pancreas, duodenum, ascending and descending colon and kidneys (7). AT responds to stimulation by extra nutrients via hyperplasia (proliferation) and hypertrophy of adipocytes (8). Excessive calories are efficiently stored in the form of neutral TGs in AT, which results in adipose hypertrophy and subsequent obesity (2,9). When adipocytes cannot uptake the excess of TGs, the body synthesizes new adipocytes (hyperplasia), which creates space for fat storage through the lipogenic pathway (9,10). In circumstances of reduction of food intake or an increase in energy expenditure, TGs from adipocytes are broken down into glycerol and fatty acids through the lipolytic pathway to provide energy. Subsequently, fatty acids and glycerol can be transported with the blood to other organs (11). Then, the lipids infiltrate into multiple ectopic organs such as the skeletal muscle, heart and liver and into the visceral adipose depots, leading to systemic low-grade chronic inflammation (12). Moreover, with progressive adipocyte expansion and obesity, the blood supply to adipocytes may be reduced, leading to hypoxia, adipocyte necrosis and macrophage infiltration into AT (13,14). During this process, AT produces and releases a variety of pro-inflammatory and anti-inflammatory factors as well, including adipokines such as leptin, adiponectin and resistin, as well as cytokines and chemokines, such as TNF-α, IL-6 and monocyte chemoattractant protein (MCP) -1 (11,14-16). The biological action of adipokine is mainly mediated by binding to their cell surface receptors on the cell membrane of target cells activating appropriate intracellular signaling pathways (2).

Obesity is defined by the National Institute of Health based on the BMI, calculated as the weight of a patient in kilograms divided by the square of height in meters, with BMI values >30 causing concern (17). Subcutaneous AT depots seem to be negatively associated with cardiovascular risk factors, while higher levels of visceral AT have been highly associated with cardio-metabolic disease (18,19). Unhealthy expansion of adipocytes is associated with abdominal obesity, promotion of the obesity-associated metabolic complications, recruitment of macrophages and other immune cells, promotion of systemic inflammation and accumulation of visceral fat (20,21). Indeed, fat accumulation intra-abdominally in men is associated with higher risk for cardiometabolic diseases, independent of BMI (22-24). In addition, abdominal visceral fat is also a strong predictor of mortality in obese women (25). A number of human studies have shown that omental adipocyte size positively associates with insulin resistance (IR) (26,27). Notably, individuals of certain ethnic backgrounds, regardless of the present country of residence and citizenship, show predisposition to central obesity and significant obesity-related medical complications (28-30). Indeed, several studies demonstrated that South Asian, Japanese and Chinese obese populations have a greater risk for IR, type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVDs) than Caucasians (31,32). Depending on the degree and duration of weight gain, obesity can progressively cause and/or exacerbate a wide spectrum of co-morbidities, including T2DM, hypertension, dyslipidemia, CVDs, non-alcoholic fatty liver disease (NAFLD), kidney diseases, respiratory disorders, sleep apnea, musculoskeletal disorders, osteoarthritis, sub-fertility, psychosocial problems and certain types of cancers (33,34) (Table I).

## 2. Obesity-related inflammation and oxidative stress (OS)

Obesity is associated with chronic low-grade inflammation in AT (35). Obesity-related inflammation is associated with the increased release of chemotactic factors, anti-inflammatory adipokines, pro-inflammatory adipokines and pro-inflammatory cytokines (Fig. 1). Inflammation of the AT in obesity is linked to a shift of the anti-inflammatory M2 macrophages in adipocytes from lean individuals to the pro-inflammatory M1 macrophages (35). In AT of lean individuals, most resident

Table I. Comorbidities caused or aggravated by obesity.

| |
|---|
| T2DM |
| Hypertension |
| Dyslipidemia |
| NAFLD |
| Cancer |
| Reproductive problems |
| CVDs |
| Mental disorders |
| Myosceletal problems-osteoarthritis |
| Psoriasis |
| Respiratory problems-sleep apnea |
| Neurogenerative problems |

T2DM, type-2 diabetes mellitus; CVDs, cardiovascular diseases; NAFLD, non-alcoholic fatty liver disease.

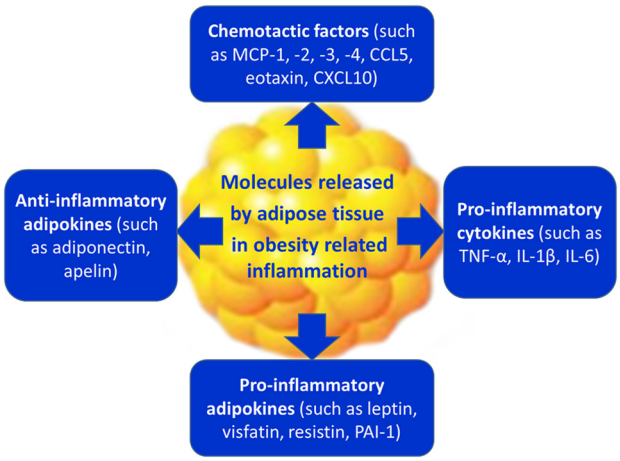


Figure 1. Schematic illustration of molecules released in obesity related inflammation and oxidative stress. MCP, monocytes chemoattractant protein; PAI-1, plasminogen activator inhibitor-1; CCL, chemokine CC motif ligand; CXCL, chemokine CXC motif ligand.

macrophages are the anti-inflammatory M2 macrophages that contribute to insulin sensitivity by secreting anti-inflammatory cytokines, such as IL-10, IL-4, IL-11, IL-13, IL-1 receptor antagonist (IL-1Ra), arginase-1 and transforming growth factor-β and anti-inflammatory adipokines, such as adiponectin and apelin (Fig. 2).

It has become evident that the presence of excessive AT enhances lipogenesis and activates the innate immune system (17,34,36-50). Compiling evidence suggests that AT, during the course of excessive fat accumulation, in obese patients, and the expansion of the fat mass, produces several chemotactic factors, such as MCP-1, -2, -3 and -4, RANTES [or chemokine CC motif ligand 5 (CCL5)], eotaxin [chemokine CC motif ligand 11 (CCL11)] and interferon γ-induced protein 10 [chemokine CXC motif ligand (CXCL10)] (17,34,36-50). In response to such stimuli, monocytes are recruited from the blood, transmigrate and infiltrate into AT depots, through adhesion processes to endothelial cells, increasing the number of activated pro-inflammatory M1

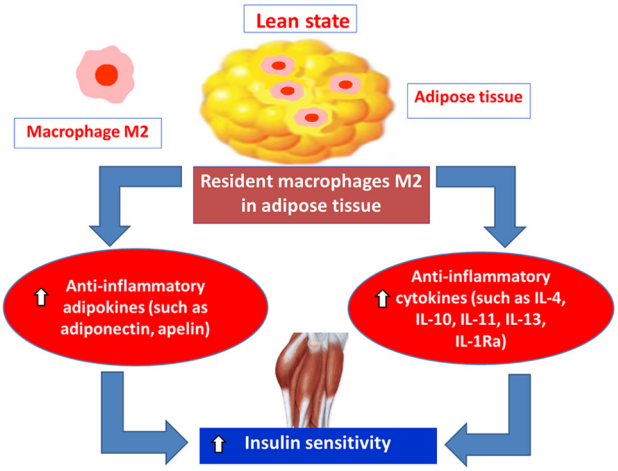


Figure 2. Schematic illustration of the permanent residency of M2 macrophages in the adipose tissue of lean subjects and their secretion. In the adipose tissue of lean subjects, most resident macrophages are polarized to the M2 anti-inflammatory phenotype, contributing to insulin sensitivity, with the secretion of (a) anti-inflammatory cytokines, such as IL-4, IL-10, IL-11, IL-13 and IL-1Ra, and (b) anti-inflammatory adipokines, such as adiponectin and apelin. IL-1Ra, IL-1 receptor antagonist.

macrophages. In turn, the growing population of pro-inflammatory M1 macrophages enhances the inflammatory changes and secretes pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6, IL-8, IL-12 and IL-23), pro-inflammatory adipokines [such as leptin, plasminogen activator inhibitor type 1 (PAI-1), visfatin and resistin] and inducible nitric oxide synthase (iNOS) (17,34,36-50). The initiation of a low-grade inflammation in AT of obese individuals contributes to an increase of leptin, visfatin, resistin and PAI-1 and to a decrease of adiponectin (17,34,36-50). This status leads to IR in adipocytes, which generates free fatty acids (FFAs) in serum, impairs glucose metabolism and favors hepatic, muscular and AT accumulation of fats and glucose (17,34,36-50). These events promote higher mitochondrial and peroxisomal oxidation, which results in the production of free radicals (FRs), OS, mitochondrial DNA injury, depletion of adenosine triphosphate (ATP) and finally, lipotoxicity (17,34,36-50). Cellular damage leads to high production of pro-inflammatory cytokines, such as TNF-α, which generates further reactive oxygen species (ROS) in tissues and increases the lipid peroxidation rate. An imbalance between the antioxidant capacity and the production of FR induces OS and promotes a systemic low-grade inflammation (17,34,36-50) (Fig. 3).

*Chemotactic factor, MCP-1.* MCP-1 or CCL2 is a 13-kDa pro-inflammatory chemokine. MCP-1 is a member of the MCP family consisting of at least four members (MCP-1, -2, -3, -4) and it exerts its action by binding to its chemokine receptor, C-C motif chemokine receptor 2 (CCR2), which is a CC motif receptor (51). The CCR2A isoform is expressed by mononuclear cells and vascular smooth muscle cells (VSMCs), while CCR2B is expressed by monocytes and natural killer cells (52). MCP-1 plays a role in the recruitment, migration and infiltration of monocytes, microglia and memory T lymphocytes to sites of infection and injury (53-56). MCP-1 is secreted predominately by macrophages and endothelial cells (52).

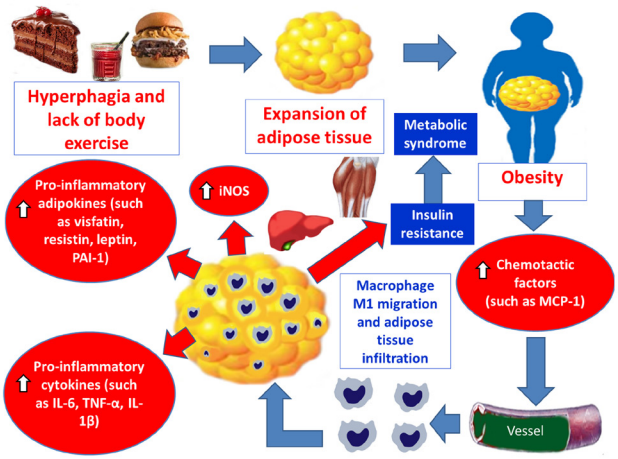


Figure 3. Schematic illustration of M1 macrophage migration and adipose tissue infiltration, in obesity, and their involvement in the pathogenesis of MetS. Overeating and lack of exercise in obese individuals causes adipocyte hypertrophy, which induces MCP-1 secretion into the bloodstream, leading to the recruitment of blood monocytes. The latter become activated M1 pro-inflammatory macrophages. M1 pro-inflammatory macrophages migrate and infiltrate adipose tissue and secrete potent pro-inflammatory cytokines, such as TNF-α, IL-6, IL-1β and IL-12, and induce iNOS production. Furthermore, M1 macrophages secrete pro-inflammatory adipokines, such as leptin, resistin and visfatin. The interplay of all these secreted pro-inflammatory cytokines and adipokines contributes to chronic low-grade inflammation in adipose tissue and to decreased secretion of adiponectin. At the same time the secreted pro-inflammatory cytokines and adipokines lead to IR in the liver and skeletal muscles, resulting in the deterioration of MetS and its chronic complications. MetS, metabolic syndrome; iNOS, inducible nitric oxide synthase; IR, insulin resistance; MCP-1, monocytes chemoattractant protein-1; PAI-1, plasminogen activator inhibitor-1.

Also, MCP-1 is produced from adipocytes and its expression is higher in visceral AT (VAT) than in subcutaneous AT (STAT). The release of MCP-1 is inhibited by adiponectin (57). There is a close relationship between MCP-1 and the number of resident macrophages in adipocytes (57-59). Plasma levels of MCP-1 are markedly elevated in obesity and T2DM (52,58,60-63). In obesity, the production of MCP-1 by adipocytes results in recruitment of monocytes and activation of macrophages, which causes AT inflammation (56,64). It has been suggested that obesity-associated inflammation in WAT is the causal factor of systemic IR (65). In addition, serum MCP-1 levels are higher in patients with atherosclerosis and the expression of mRNA MPC-1 is increased in atherosclerotic lesions as well (66-68). Also, inhibition of MPC-1 expression or its receptor (CCR2) reduces the extent of atheroma formation in hypercholesterolemic mice (55,66,69-71).

*Anti-inflammatory adipokines-adiponectin as a biomarker of AT.* Adiponectin belongs to adipokines and is a 30-kDa peptide secreted only by AT and in particular in large amounts by adipocytes of white AT (2,72-74). It acts via two receptors (ADIPOR1 and ADIPOR2) that elicit AMPK signaling and may be modulated by T-cadherin (75). Adiponectin has been described as a main anti-inflammatory adipokine (76). Its anti-inflammatory actions are partly due to its ability to reduce TNF-α activity, via suppression of adiponectin-induced NFκB (77). Also, adiponectin was shown to directly decrease production of pro-inflammatory cytokines TNF-α and IL-6 by macrophages (78). Additionally, adiponectin inhibits generation of ROS induced by high glucose and oxidized low-density lipoprotein (LDL) via a cAMP/PKA-dependent pathway (48,79,80). High ROS levels in adipocytes suppress adiponectin expression and secretion (81,82). Accordingly, there is an inverse association between human serum adiponectin levels and systemic OS (83). Adiponectin increases insulin sensitivity in multiple tissues via up-regulation in insulin signaling. This insulin-sensitizing effect of adiponectin seems to be mediated by increased fatty acid oxidation through AMP-activated protein kinase and peroxisome proliferator-activating receptor-α (PPARα) activation (84,85). In addition, adiponectin reduces glucose content in tissues, by trasfering cytoplasmic glucose trasporter type 4 (GLUT4) toward the surface of the cytoplasmic membrane (73). Also, adiponectin inhibits gluconeogenesis within the liver (86). Adiponectin exhibits cardiovascular protection by suppressing inflammatory processes occurring in the early phases of atherosclerosis and microangiopathy through inhibition of the adhesion of monocytes to blood vessel endothelial cells, as a result of down-regulated expression of adhesion proteins, decreasing of the transformation of macrophages into foam cells and down-regulating intimal smooth muscle cell proliferation (2,48,77,87-91). It also enhances nitrogen oxide (NO) synthesis in endothelial cells and stimulates angiogenesis (73,80,92,93).

Adiponectin synthesis is regulated by insulin and insulin-like growth factor-1, which leads to increased concentration of this adipokine (73,94). However, its synthesis is inhibited by pro-inflammatory cytokines, such as TNF-α and IL-6. This suggests that obesity and IR are important factors contributing to low levels of serum adiponectin (95). Also, low serum levels of adiponectin are found in obese, insulin-resistant individuals with related pathologies including T2DM, dyslipidemia and CVDs (89,93,96-99). On the other hand, weight loss increases adiponectin concentrations (73). Hence, elevated levels of adiponectin may lead to the decrease in the risk of T2DM (100).

*Apelin as a biomarker of AT.* Apelin is a short peptide hormone, which belongs to adipokines and is produced by adipocytes in proportion to the present amount of fat; it plays an important role in energy metabolism and is considered to be linked with obesity and diabetes (39,101,102). Apelin exerts its effects by binding with angiotensin II protein J (APJ) receptor (101,103). Apelin promotes brown adipocyte development through the phosphatidylinositol 3-kinase (PI3K)/Akt and AMPK signaling pathways (102). Also, apelin is able to increase the browning in white adipocytes (102,104). In addition, it has been found that apelin relieves the TNF-α suppression on brown adipogenesis (102). Apelin stimulates glucose uptake, increases insulin sensitivity and regulates lipolysis and fatty acid oxidation (101). It has been found that serum apelin levels are increased in obesity. This may be due either to potential resistance to apelin or to its attempt to delay or reduce tissue IR (105). Nevertheless, current literature suggests that apelin administration protects diabetic and/or obese mice (101) by lowering glucose levels and hence, it may have a therapeutic role against obesity and related metabolic diseases (104). Apelin with its activity on enthothelial APJ receptors may additionally improve nitric oxide (NO) release

and endothelium-dependent vasodilation (39,106). Apelin has antioxidant effects because it suppresses ROS production and release in AT and improves the antioxidant state in OS-related conditions (107). Apelin promotes the synthesis of antioxidant enzymes via Ras/Raf/mitogen-activated protein kinase (MAPK)/ERK and AMP-activated protein kinase (AMPK) pathways (104), suppresses the expression of pro-oxidant enzymes via the same pathway, and increases mitochondrial oxidative capacity (104,108-111).

*Pro-inflammatory adipokines and their relationship with obesity*

*Leptin*. Leptin belongs to adipokines and is a 16-KDa peptide, encoded by the obese (ob) gene. It is mainly secreted by WAT and its secretion increases according to the volume of AT and to the TGs stored in adipocytes (2,48,112-116). When body energy stores are adequate, leptin suppresses food intake, regulating appetite, energy balance and causing satiety (2,48,112-114). The sensation of satiety of leptin is achieved by crossing the blood-brain barrier and targeting the hypothalamus (2,112,117-119). Hypothalamic leptin signaling is mediated by leptin receptor and downstream processes, including JAK2/STAT3 pathway (120). However, obesity is associated with increased leptin protein and mRNA levels compared with lean controls. The failure of the elevated leptin levels to correct the metabolic complications seen in obesity, is mainly related to leptin resistance, in tissues with decreased sensitivity to leptin (3,35,39,121-123). The influence of leptin on IR is not yet fully understood (35). However, it has been found that IR is associated with elevated serum leptin levels (35). A possible explanation is that leptin resistance causes reduction of lipid oxidation, which leads to lipid accumulation and IR (124,125). Also, leptin in obese humans causes an increase in blood pressure, through sympathetic activation at vascular and/or renal levels (126). Leptin has pro-inflammatory actions, which are related to structural and functional similarities with the cytokine IL-6 (115). Also, leptin promotes OS and endothelial cell dysfunction and activation, increases phagocytic activity by macrophages and induces the production of pro-inflammatory cytokines such as TNF-α, IL-6, IL-2 and IL-1 (2,127,128). In addition, it has been found that leptin administration increases c-reactive protein (CRP) levels, which confirms further its inflammatory effects (123).

*Visfatin*. Visfatin also known as nicotinamide phosphoribosyltranferase and pre-B-cell colony enhancing factor (129,130) is a 52 kDa adipokine, which is predominantly expressed in human VAT (131), an area of fat tissue, whose accumulation is strongly associated with an enhanced cardiovascular (CV) risk (48,129). Visfatin is also secreted by macrophages, bone marrow, skeletal muscles and various organs including the liver, lungs, brain, heart and pancreas (49,129). However, a specific receptor for visfatin has not been identified yet (93). Several authors have suggested that visfatin levels increase with obesity, T2DM, MetS or CVDs (132-134). However, other studies have shown conflicting results regarding the relationship of visfatin with MetS (135,136). It has been found that weight loss decreases visfatin levels in obese patients (134). Moreover, leucocytes from obese patients produce higher amounts of visfatin compared with lean patients (137). Visfatin levels beyond a threshold appear to be associated with IR and obesity-related vascular disorders (130,138). Specifically, visfatin appears to contribute to the release of pro-inflammatory cytokines IL-1β, IL-6, IL-8 and TNF-α, through a regulation of the JAK2/STAT3 and IKN/NF-kB signaling pathways, promoting inflammation (129,131,139-144). Moreover, in experimental studies, it has been found that visfatin induces endothelial dysfunction, via the NF-κB pathway, in the vascular endothelium and promotes the proliferation of human VSMCs (129,138). Additionally, visfatin induces NF-κB pathway dependent OS, and blockade of this pathway, via selective IκB Kinase (IKK-2) inhibition, leads to a partial reduction in OS, which it is independent of the MAPK/ERK signaling pathway (138,145).

*Resistin*. Resistin is a 12.5 kDa adipokine, which in human AT is secreted predominantly in macrophages (93). Resistin is also known as adipocyte-secreted factor or Found in Inflammatory Zone 3 (93). The resistin receptor remains unknown, but resistin binding to the Toll-like receptor 4, adenylyl cyclase-associated protein 1 receptor and G protein-coupled receptors was proposed to mediate resistin inflammatory responses in human cells (93,146,147). Resistin has also been associated with the inflammatory response, by promoting activation of the pro-inflammatory cytokines IL-6, IL-1β and TNF-α (16,131,148-150). Moroeover, resistin upregulates several adhesion molecules, through NF-κB, in vascular endothelial cells (148,151). In animal models, resistin promotes IR, but in humans there are conflicting reports about the potency of resistin in metabolic diseases (93,152,153). Several studies indicated that increased serum resistin levels are associated with increased obesity, visceral fat, IR and T2DM (154-157), while other studies failed to reach to such conclusions (158,159). Also, resistin generates OS, which activates MAPK signaling and inhibits endothelial nitric oxide synthase (eNOS) gene expression (160). Moreover, resistin reduces NO production, by inducing the proliferation of VSMCs, and causes endothelial dysfunction (160). In turn, reduction of NO availability results in impaired vasodilation, increased vascular permeability, endothelial cell adhesion and damage leading to CVDs (160,161).

*Plasminogen activator inhibitor-1 (PAI-1)*. PAI-1, also known as SERPINE1 is a physiological inhibitor of tissue plasminogen activators (tPAs) (162). Increased PAI-1 activity is associated with reduced fibrinolytic activity and thus, increased risk for thrombus formation and CVDs (163). PAI-1 is synthesized in AT, especially in visceral fat, as well as in preadipocytes, fibroblasts, vascular endothelial cells and in immune cells (2,163-165). Increased PAI-1 plasma levels have been found in obese patients and reduced levels were achieved with weight loss (129,166). In experimental studies, using obese mouse models with MetS, it has been found that the deletion of PAI-1 inhibited carotid artery atherosclerosis (167), while pharmacological PAI-1 inhibition attenuated atherosclerosis by inhibiting macrophage accumulation and eliminating senescent cells in the atherosclerotic plaques (168). In human studies, PAI-1 was found to be associated with IR, MetS and atherosclerosis in obesity (163,169). Also, in animal studies using mice fed with a high-fat diet, a deficiency of PAI-1 led to

a decrease of body weight gain and improvement of IR (170). In addition, adipocyte hypertrophy in obesity may create local hypoxic areas, which activates hypoxia-inducible factor-1α (HIF-1α). The increase in HIF-1α causes an increased expression of several pro-inflammatory cytokines, such as TNF-α, IL-6, IL-1β and ROS, leading to higher PAI-1 expression in adipocytes (171).

*Pro-inflammatory cytokines and their relationship with obesity*

*TNF-α*. TNF-α is a 26-kDa pro-inflammatory cytokine produced by macrophages, adipocytes and vascular endothelial cells, in response to chronic inflammatory activity (37,85,172,173). TNF-α exists in two forms, membrane-bound (mTNF-α) and free soluble (fTNF-α). TNF-α is synthesized as a transmembrane monomer, which afterwards can be cleaved by TNF-α converting enzyme, to yield the 17-kDa soluble form (52). Both forms exist as trimers that have biological activity. TNF-α has two distinct TNF-α receptors, TNF-R1 and TNF-R2, that are similar in their extracellular ligand-binding domains but differ markedly in their intracellular signaling domains (52,85). The majority of signaling in AT is downstream of the TNFR1 (52). TNF-α is a pro-inflammatory cytokine characterized by various biological effects including metabolic, inflammatory, proliferative and necrotic (173). TNF-α directly impairs peripheral glucose uptake, by increasing serine phosphorylation of insulin receptor substrate 1 (IRS-1), inhibits GLUT 4 translocation to the plasma membrane and results in peripheral IR (173,174). TNF-α also potentially increases lipolysis in human adipocytes by regulating hormone-sensitive lipase in adipocytes, resulting in increased circulating FFA levels and peripheral IR in obesity (173). Expression of TNF-α is increased in obesity and IR in humans (37), whilst treatment with TNF-α induces IR in AT (48). Serum TNF-α levels are decreased during weight loss (175). TNF-α is a part of a complex inflammatory network and is capable of initiating cytokine cascade activation that involves both synergistic and inhibitory reactions, which control the synthesis and expression of other cytokines, hormones and their receptors (176). ROS production can also be induced by TNF-α binding to its TNF-R1 receptor promoting NF-κB, ERK, p38MAPK and FADD/pro-caspase-8 signaling pathways (177-179). TNF-α causes systemic acute-phase response via the release of other pro-inflammatory cytokines, such as IL-6 and the reduction of anti-inflammatory adiponectins (48). TNF-α also increases the induction of OS and the production of superoxide anions (180).

*IL-1β*. IL-1β is a 31-kDa pro-inflammatory cytokine, secreted by M1 macrophages (181). It is produced as pro-IL-1β, a pro-inflammatory cytokine, which becomes biologically active by cleavage, requiring the protease caspase-1 (182), which is activated through the NLRP3 inflammasome complex (183). Obesity appears to be directly related to the deregulation of IL-1β expression and the increase in its levels. The increased IL-1β levels contribute to the induction of chronic inflammatory diseases (184). High levels of IL-1β promote ectopic fat accumulation, recruitment of immune cells to AT and liver, fibrosis, IR, T2DM and atheromatous plaque formation in obese patients (181,184). In particular, the increase in IL-1β levels, in STAT, contributes to the suppression of PPARγ expression and the inhibition of the differentiation of preadipocytes to mature adipocytes. However, there is a discrepancy about the effects of IL-1β on lipogenesis and lipolysis (185-188). High levels of IL-1β are observed in the VAT of obese individuals (189,190), leading to reduced TG storage in WAT and hepatic steatosis (184). In parallel, high levels of IL-1β in AT are associated with extracellular matrix (ECM) disorganization, diminishing AT hyperplasia (191) and provoking fibrosis and inflammation (192). Elevated IL-1β levels contribute to high immune cell recruitment, promote local inflammation via increase in expression of VCAM-1, ICAM-1, MCP-1 and suppression of PPARα (193). Moreover, the increased recruitment of immune cells is responsible for the hepatic cirrhosis promotion (184). IL-1β contributes to an increase in PAI-1 secretion and promotes fibrosis and chronic liver disease (194). IL-1β appears to lead to activation of the serine/threonine kinase, janus kinase (JAK) 1, which inactivates IRS1 and IRS2 (184), downregulates the expression of PI3K, p85, pAkt and GLUT4, leading to suppression of insulin signal transduction, with a subsequent increase in blood glucose levels (195). Elevated FFAs bind to receptors in the liver, activating the IKK/NFκB pathway and stimulating increased IL-1β expression (196). Respectively, high glucose levels stimulate NADPH oxidase, ROS production and thioredoxin-interacting protein expression, that binds to NIPR3 (196) and activates IL-1β production. As a result, IL-1β binds to the IL-R1 receptor on pancreatic β-cells and leads to increased expression of cytokines and chemokines (197), facilitating the accumulation of hematopoietic cells, such as macrophages, which secrete pro-inflammatory cytokines that further exacerbate the inflammation cascade causing impairment of insulin secretion (184). High IL-1β concentration is further capable of leading to pancreatic β-cell apoptosis by the NF-κB pathway regulation and FAs overexpression (198), or through the depletion of calcium ions ($Ca^{2+}$), in the c-Jun N-terminal kinase (JNK)-mediated endoplasmic reticulum (ER) with the mediation of JNK (199). Finally, IL-1β enhances the proliferation and migration of VSMCs promoting the atherosclerotic plaque development (184).

*IL-6*. IL-6 is produced by numerous different cell types, including adipocytes, endothelial cells, pancreatic β-cells, macrophages and monocytes (14,200-202). There are two signaling pathways for IL-6 including its classical signaling mechanism involving the binding of IL-6 to its receptor complex (IL6-Ra) that subsequently interacts with an IL-6ST signaling protein (also known as glycoprotein 130, gp130) at the plasma membrane, and the non-classical signaling mechanism which is related to the interaction of the IL-6ST protein with a soluble form of the IL-6-binding receptor (203). Both IL-6 signaling pathways lead to activation of the JAK1-STAT3 pathway (203). Its actions can be beneficial or harmful to the organism, depending on the site of action, the magnitude of production and the duration of the response (204,205). In summary, its beneficial actions are related to its production by skeletal muscles, in response to physical exercise, contributing to lipid metabolism and enhancement of insulin sensitivity in muscles (204,205), as well as appetite suppression (206).

Other actions of IL-6 include immune response and hematopoiesis (14,200-202). It participates in the regulation of neural differentiation, maturation and function and in energy homeostasis (14,200-202). In obesity, serum IL-6 levels are elevated and 10-35% of IL-6 produced is attributed to WAT (207). In obesity, high caloric intake in combination with reduced energy expenditure is directly related to changes in the physiology and morphology of WAT (207). In particular, WAT expansion is observed through an increase in the number or size of adipocytes (208,209). Therefore, in the WAT of obese patients there is an infiltration of immune cells, including T cells and macrophages (19). Both adipocytes, as well as immune cells in WAT, are the main sources of increased circulating IL-6 levels. The VAT secretes a number of substances that further promote IL-6 expression and releases ~2-3 times more IL-6 concentrations than STAT (19). Chronic exposure to high serum IL-6 levels has been associated with an elevated likelihood of impaired glucose tolerance, T2DM, high blood pressure and obesity (48), while is also positively associated with IR in obesity (210,211). Furthermore, exogenous IL-6 administration causes IR in humans, while weight loss results in IL-6 decrease and bariatric surgery improves IR (212-215). Thus, if the elevated plasma IL-6 levels in obesity are considered, it could be suggested that chronic low-grade inflammation in obesity links IL-6 as causal factor for IR through the progressive tissue-infiltration by immune cells (216).

## 3. Obesity, OS and insulin resistance (IR)

Insulin is an anabolic, peptide hormone, secreted by the pancreatic β-cells of the islets of Langerhans, in response to high blood glucose levels and controls the metabolism of carbohydrates, proteins and fats by stimulating the absorption of glucose from the blood into lipid cells, skeletal muscle cells and the liver, for ATP production or storage as glycogen and TGs (217). More specifically, in fed states, the exogenous glucose uptake increases the circulating glucose levels and stimulates insulin secretion (123,217,218-220). Also, other nutrients from food such as FAs and amino acids increase insulin secretion, which stimulates lipogenesis and protein synthesis (218,221). Under fasting conditions, lipolysis is induced from stored TGs in AT and supplies i) glycerol for hepatic glucose production (gluconeogenesis) and ii) FAs for β-oxidation (2,220). In the liver, insulin suppresses hepatic gluconeogenesis (220). Also, insulin reduces the rate of breakdown of glycogen in muscles and liver (glycogenolysis), retaining normal glucose levels (222). Regarding the effect of insulin on lipid metabolism, insulin inhibits lipolysis (antilipolytic action), increases hepatic lipid synthesis for subsequent TGs storage in AT (223) and stimulates glucose uptake into the skeletal muscles, heart and AT (220). In order to exert its effects, insulin binds to its receptor (IF), a tyrosine kinase receptor. A reduction in insulin signaling triggers IR that could affect the metabolic actions of insulin (224). If a decrease of the blood glucose levels is not achieved by insulin, then pancreatic β-cells increase insulin release resulting in hyperinsulinemia, which is the key for IR (225). Therefore, hyperinsulinemia often precedes the development of marked IR and fat mass gain (226).

Insulin signaling is initiated by the phosphorylation/activation of the cytoplasmatic insulin tyrosine kinase receptor that is associated with the activation of two main signaling pathways: i) PI3K/AKT [also known as protein kinase B (PKB)] pathway; and ii) the MAPK pathway (2,227). In healthy subjects, by simultaneously stimulating these distinct pathways (PI3K and MAPK), insulin couples metabolic and hemodynamic homeostasis.

*PI3K/AKT2 signaling pathway (also known as protein kinase B or PKB).* In the PI3K-AKT/PKB pathway the binding of insulin to its cell surface receptor activates the lipid kinase, PI3K, binding to its Src homology 2 domain, which activates several phosphatidylinositol-(3,4,5)-triphosphate-dependent serine/threonine kinases, including AKT/PKB (2). Ultimately, these signaling events result in the translocation of the insulin-dependent GLUT4 from its cytoplasmic storage vesicle to the plasma membrane, leading to an increase in glucose uptake (2). The PI3K-AKT signaling pathway regulates the metabolic insulin actions by promoting glucose utilization, protein synthesis and lipogenesis (228).

*MAPK pathway.* MAPK activation triggers a cascade that regulates the effects of insulin on mitogenesis, growth and differentiation and is not implicated in the metabolic actions of insulin (2). Also, MAPK-dependent insulin signaling pathway controls secretion of the vasoconstrictor, endothelin-1, from endothelium (63).

*IR.* When a decrease of blood glucose levels is not achieved by insulin, then pancreatic β-cells increase the release of insulin, resulting in hyperinsulinemia, which is the key for IR (224,225). Therefore, hyperinsulinemia often precedes the development of marked IR and fat mass gain (226,229) (Fig. 4). The IR in AT, skeletal muscles and liver is commonly linked with obesity, which is a pathophysiological factor of T2DM (230-233). When IR develops in fat tissues, insulin-mediated inhibition of lipolysis is impaired leading to increased lipolysis (123,234) (Fig. 4). The resulting increase in circulating FAs in turn worsen IR, causing alterations in the insulin signaling cascade in different organs, thus creating a vicious cycle (235,236) (Fig. 4). Moreover, in IR, there is a reduced insulin ability to suppress glycogenolysis in hepatocytes and myocytes (234). In IR, FFAs, in muscles, affect IRS-1-associated PI3K activity, leading to decreased GLUT4 translocation to the surface and reduced glucose uptake (235). In parallel, in IR the FFAs act on the liver to promote gluconeogenesis. Therefore, insulin-resistant individuals fail to inhibit hepatic glucose production and hyperglycemia. This results in a hyperinsulinemic state to maintain normal glucose levels (123). However, this compensation eventually fails, leading to decreased insulin levels, which is further exacerbated by the lipotoxic effect of FFAs on pancreatic β-cells (123,236,237). Additionally, in IR, the FFAs act on the liver and promote lipogenesis (Fig. 4). It is essential to note that visceral lipolysis increases the supply of FFAs, directly to the liver, via the splanchnic circulation, thus making visceral fat deposits more important contributors to IR than subcutaneous fat (123). Together with this, there is increased *de novo* hepatic TG synthesis and a disruption of β-oxidation in hepatic mitochondria (238-241). This net leads to increased hepatic very low-density lipoproteins (VLDLs) secretion and hypertriglyceridemia (238-241). The hepatic accumulation of

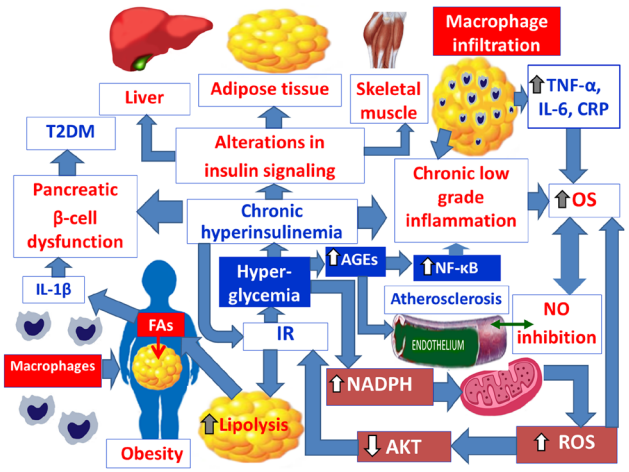


Figure 4. Schematic illustration of the pathways associated with the development of T2DM in obese individuals. The cellular mechanisms involved in the pathogenesis of obesity-associated T2DM include: i) Alterations in the insulin signaling in metabolic tissues, such as liver, adipose tissue and skeletal muscles; ii) pancreatic β-cell dysfunction; and iii) chronic low-grade inflammation and increased oxidative stress. Obesity causes IR and hyperglycemia. Hyperglycemia causes glucotoxicity and an increase in AGEs, resulting in the up-regulation of NF-κB, which is a mediator of inflammation and immunity. Increased AGEs affect vascular endothelium and block the activity of NO. The inhibition of NO enhances the oxidative stress. Additionally, glycotoxicity induces the glycolysis and the Krebs cycle resulting in an increased flow of NADPH and FADH2, that act as electron donors to the mitochondrial chain, resulting in an excess of electrons in coenzyme Q and the production of mitochondrial superoxide, resulting in an increase in ROS. Chronic exposure to high intracellular ROS levels in adipocytes ultimately causes mitochondrial dysfunction and perpetuates adipose tissue inflammation, resulting in IR and T2DM. In addition, peroxide-induced OS, causes impairment of the AKT, which results in IR and T2DM. Also, chronic hyperglycemia causes alterations in IR in the liver, adipose tissue and skeletal muscles. Furthermore, chronic hyperglycemia creates chronic low-grade inflammation, which increases OS. The increased FAs cause lipotoxicity and increase the secretion of IL-1β, which is responsible for the deficiency of insulin secretion from pancreatic β-cells resulting in IR and T2DM. Moreover, infiltration of adipocytes by macrophages causes an increase in TNF-α and IL-6. The increase in TNF-α is responsible for tissue inflammation, generation of ROS and IR propagation in peripheral tissues and adipocytes, which is important for the onset of T2DM. In addition, the increase in IL-6 levels contributes to indirect prevention of insulin binding to its receptor, as well as the induction of CRP, which like TNF-α, is associated with IR and T2DM. T2DM, type 2 diabetes mellitus; IR, insulin resistance; AGEs, advanced glycation end products; NO, nitric oxide; FADH2, flavin adenine dinucleotide (reduced form); ROS, reactive oxygen species; FAs, fatty acids; CRP, c-reactive protein.

TGs and the toxic levels of FFAs results in hepatic lipotoxicity (238-241). This mechanism contributes to the production of ROS and the development of NAFLD, which is associated with the development of MetS, which may progress to the more serious non-alcoholic steatohepatitis (NASH) with subsequent hepatic fibrosis, cirrhosis and cancer (225,242). In fact, there is a by-directional relationship between obesity-related IR and NAFLD, since obesity-related IR causes fatty liver and excessive hepatic fat accumulation, promotes IR and weight gain (243). In addition, high concentrations of FFAs increase cholesterol esters and triglyceride (TG) synthesis and subsequently the production of VLDLs rich in TGs (244,245). These in turn, activate cholesterol ester transfer protein, promote TG transfer from VLDL to high-density lipoprotein (HDL), increase HDL clearance and decrease its concentrations (244,245). Moreover, triglyceride-rich LDL, formed after exchange with LDL cholesterol ester, becomes hydrolyzed by lipoprotein lipase or hepatic lipase, leading to cholesterol-depleted small dense LDL particles (244,245). All these alterations in lipoprotein concentrations constitute the hallmark of atherogenic dyslipidemia, caused by IR, in MetS (244,245). Another contribution of IR to MetS is the development of hypertension caused partly by the loss of the vasodilatory effect of insulin and by FFA-induced vasoconstriction due to ROS production and the subsequent scavenging of NO (246). Other mechanisms involve the increased sympathetic stimulation and the renin-induced sodium reabsorption in the kidneys (247). Finally, the contribution of IR, to the promotion of atherogenic processes and the increase of CVD risk, is the development of a higher serum viscosity and a pro-thrombotic state, caused by the increased levels of fibrinogen and PAI-1 (34,165,169,248-253). IR and IL-6 produced during the acute phase reaction contribute to elevated fibrinogen concentrations (34,254). Fibrinogen is synthesized by hepatocytes and holds a pivotal role in the coagulation cascade, being a major determinant of plasma viscosity and platelet aggregation, whilst potentially plays a pro-inflammatory role in vascular wall disease (34,254,255). In parallel, PAI-1 is elevated in IR, obesity and MetS (34,256). PAI-1 regulates the endogenous fibrinolytic system and constitutes the main inhibitor of fibrinolysis by binding and inactivating the tPA (34,248,257-260). Therefore, elevated PAI-1 levels lead to decreased clearance of clots (34,248,257-260). Enhanced AT expression of PAI-1 has been reported in obesity, particularly in VAT (34,261), whilst there is an inverse relationship between PAI-1 activity and adiponectin in overweight and obese women (34,259,260).

## 4. Obesity, OS and metabolic syndrome (MetS)

MetS is a complex disorder defined by a cluster of clinical and metabolic conditions that occur together and increase the risk for IR, T2DM, dyslipidemia, CVDs, prothrombotic state and stroke (262-264). According to the International Diabetes Federation (IDF), metabolic syndrome (MetS) is characterized as the presence of three or more of the following features: i) obesity; ii) hyperglycemia; iii) hypertension; iv) low HDL cholesterol levels; and/or v) hypertriglyceridemia (263). Obesity is the most frequently observed component of MetS (265). It has been established that patients with MetS are five times more likely to develop T2DM and have a 2-3 times higher risk of CVDs (stroke and myocardial infarction), compared with healthy subjects (264,266,267). In addition, MetS has been associated with other clinical conditions, such as hepatic steatosis and NAFLD, hypogonadism, polycystic ovarian syndrome, obstructive sleep apnea, vascular dementia, Alzheimer's disease and carcinomas, especially breast, pancreatic and colorectal cancers (218,268,269). Obesity is the most frequently observed component of MetS (265). The IDF estimates that MetS affects almost a quarter of the adult general population in Western societies (269-271). The prevalence of MetS in men does not differ before and after 50 years of age, but women >50 years, show a sharp increase in prevalence (272). It is associated with higher mortality risk in younger adults than in elders (273). Accumulating evidence indicates that dysregulation of the production a wide range of adipocytokines and cytokines, due to excessive accumulation of

body fat, participates in the pathogenesis of obesity associated MetS (128,163,169). The link between PAI-1 and MetS with obesity is well established. Increased PAI-1 serum levels are associated with the development of IR, MetS, atherosclerosis and thrombosis in obese patients (128,163,169). Treatment with TNF-α contributes to the development of IR in AT (175). In patients with MetS, chronic exposure to increased IL-6 levels is related to the development of IR by depletion of GLUT4 and disruption of insulin signaling (210,211). Leptin is also involved in the pathophysiology of MetS (274). High plasma levels of leptin are directly associated with IR, MetS and lipid accumulation due to leptin resistance (35,39,124,125). Moreover, visfatin plays a central role in MetS. Elevated visfatin serum levels are associated to IR, T2DM and decreased function of pancreatic β-cells (129,275). Conversely, a protective role of adiponectin against MetS has been reported, since it directly attenuates production of IL-6 and TNF-α, by macrophages, through its ability to suppress NF-κB activation (78,276). In addition, apelin reduces MetS risk. It has been demonstrated that apelin stimulates glucose uptake, increases insulin sensitivity and regulates lipolysis in patients with MetS (101). OS is also critically involved in the pathogenesis of MetS and in the progression of its complications (277-280). In patients with MetS there are higher levels of oxidative markers, as well as reduced antioxidant defenses (277). In obesity, the chronic low-grade inflammation, produced by adipocytes exacerbates OS (35) (Fig. 4). Visceral fat accumulation induces an increase in mitochondrial and peroxisomal oxidation of FAs, and the production of ROS (35,281,282). Furthermore, visceral fat accumulation causes over-consumption of oxygen, which generates FRs in the mitochondrial respiratory chain (35,281,282). In addition, a lipid-rich diet can alter oxygen metabolism and generate ROS (35,281,282). Moreover, high ROS production and a decrease in antioxidant capacity leads to a reduction in the bioavailability of vasodilators, particularly NO, and an increase in endothelium-derived contractile factors, favoring atherosclerotic disease (35,281,282) (Fig. 4). With regards to hypertension, elevated OS, in vascular wall leads to vasoconstriction, vascular remodeling, inflammation and fibrosis which results in hypertension and atherosclerosis (268,277,283). Regarding NAFLD, it has been documented that elevated OS appears to be a key mechanism in promoting liver injury and liver inflammation in NAFLD (284). Finally, it has been found that dyslipidemia is associated with higher ROS release and lower eNOS synthesis (277).

## 5. Obesity, OS and T2DM

T2DM is a heterogeneous, chronic metabolic disorder, characterized by elevated blood glucose levels with a high prevalence, up to 90%, of all diagnosed diabetic cases in adults (285,286). IR leads to hyperglycemia and over time to T2DM (286). It has been found that the relative risk of T2DM, in adult men and women, increases for a BMI, >24 kg/m$^2$ in men, and 22 kg/m$^2$ in women (34). Women with T2DM are 3-4 times more prone to CVDs compared with 2-3 times in men with T2DM (287). Obesity is an important independent risk factor for IR and T2DM (288-291). IR is responsible for the development of hyperglycemia and over time may evolve to T2DM. IR alone is not capable of causing an increase in blood sugar (292), since the pancreas has mechanisms to adapt, by increasing the mass of β-cells and the ability to produce insulin (292,293). Thus, despite reduced peripheral insulin sensitivity, blood sugar levels could retain stable (292). The cellular mechanisms involved in the pathogenesis of obesity-associated T2DM include: i) alterations in the insulin signaling; ii) pancreatic β-cell dysfunction and failure; and iii) chronic low-grade inflammation and increased OS (294). The mechanisms interrelating obesity to the pathogenesis of T2DM are depicted in Fig. 4. Obesity causes generalized IR in AT, liver and skeletal muscles and is associated with increased insulin secretion and chronic hyperinsulinemia, which promotes further weight gain (292,295,296). Therefore, there is a bi-directional relationship between obesity and hyperinsulinemia. Insulin resistant conditions in T2DM could be caused by signaling defects at a number of levels of the insulin-signaling cascade in metabolic tissues, such as liver, AT and skeletal muscles (292,243,297). In addition, in IR and T2DM, the liver fails to suppress glycogenolysis and gluconeogenesis, despite compensatory hyperinsulinemia, and is associated with accelerated glucose synthesis and fasting hyperglycemia (292,243,297). In T2DM, the IR in skeletal muscles is associated with postprandial hyperglycemia, since in these patients, skeletal muscles exhibit decreased insulin sensitivity, which results in impaired insulin-stimulated glucose uptake (298). As aforementioned, IR does not necessarily imply T2DM. A harmful mechanism for the functionality of β-cells is 'glucotoxicity'. Glucotoxicity is dependent on the duration and degree of hyperglycemia, in which the elevated glucose levels, characteristic of T2DM, contribute to desensitization of pancreatic β-cells in insulin secretion (292,294). Another mechanism that contributes to further loss of β-cells and pancreatic dysfunction is 'lipotoxicity'. It is directly related to fat occuring obesity and is accompanied by an underlying predisposition to T2DM and increased serum FFA levels (292,299). FFAs are elevated in the plasma of patients with T2DM, due to uncontrolled lipolysis, by insulin-sensitive lipase, in adipocytes (300). The high levels of FFAs impair the function of pancreatic β-cells and the glucose-induced insulin secretion (300) (Fig. 4). Another mechanism, related to the disruption of pancreatic β-cells, is their low antioxidant defense, since they do not express, in high ratio, antioxidant enzymes, which make them susceptible to oxidative damage (301). Finally, due to the accumulated fat during obesity, increased levels of cytokines from macrophages are observed, such as IL-1β (302), which is also responsible for the deficiency of insulin secretion from β-cells (34) (Fig. 4). In addition to BMI, there is a strong association between abdominal obesity (central obesity) and the incidence of T2DM (24,303-308). Abdominal obesity is associated with the following conditions that may lead to systemic inflammation and IR: i) increased levels of glucose and non-esterified fatty acids; ii) hormonal imbalance with increased leptin levels and decreased adiponectin levels; and iii) increased secretion of cytokines and pro-inflammatory substances from fat cells (309,310). In more detail, in terms of the secretion of cytokines and pro-inflammatory substances from adipocytes, the driving force is the excess visceral fat that triggers the cascade of inflammation (309,310). In response to the secretion of these substances, mononuclear cells migrate from blood circulation to the AT, and they differentiate into

macrophages (309,310). Macrophages secrete cytokines, thus in obesity an increased secretion of TNF-α and IL-6 is observed (309,310) (Fig. 4). Secretion of TNF-α is responsible for tissue inflammation, due to its role in the generation of ROS, and activation of transcription-induced pathways, and for IR, in peripheral tissues and adipocytes, which is important for the onset of T2DM (309,310). The increase in IL-6 levels contributes to the prevention of the binding of insulin to its receptor, through the induction of proteins associated with it (310-312), as well as the induction of CRP, which like TNF-α, is associated with IR (309,310) (Fig. 4). Additionally, hyperglycemia, characteristic in T2DM, is associated with the generation of advanced glycation end products (AGEs), binding to their receptors. AGEs are responsible for the up-regulation of the transcription factor NF-κB, which is a mediator of inflammation and immunity (313), while AGEs also block the activity of NO in the vascular endothelium and promote the production of ROS (313) (Fig. 4). Finally, a key role for chronic inflammation and OS in obesity related T2DM is mitochondrial dysfunction (314-316). Specifically, due to the increased concentration of sugars, glycolysis and the Krebs cycle are induced and cause an increased flow of NADH and FADH2 (flavin adenine dinucleotide; reduced form) (314-316). They act as electron donors to the mitochondrial chain, resulting in the accumulation of electron donors in coenzyme Q (314-316). This results in the production of mitochondrial superoxide radical (FR), an important source of ROS from adipocytes (314-316). Chronic exposure to high intracellular ROS levels in adipocytes ultimately causes mitochondrial dysfunction and perpetuates AT inflammation, together with impairment of the AKT signaling pathway that induces IR (314-316) (Fig. 4).

## 6. Therapeutic interventions on inflammatory mediators for the therapy of obesity-associated metabolic diseases

*Treating inflammation by blocking IL-1R*. In patients with T2DM, the high blood glucose levels induce cytokine IL-1β production and secretion, in the β-cells of the pancreatic islets of Langerhans, leading to pro-inflammatory immune responses, β-cell dysfunction, decreased β-cell proliferation and increased β-cell apoptosis (198,317,318). Therefore, short-term IL-1 receptor (IL-1R) blockage could lead to improvements in both metabolic and inflammatory parameters in patients with MetS and T2DM and may represent a potential targeted therapeutic approach for these patients. For instance, Larsen *et al* tested the effects of anakinra therapy in two studies (319,320). In their first study, Larsen *et al* (319) examined the effects of anakinra treatment, in a double-blind, parallel-group trial with 70 patients with T2DM, that were randomly assigned to receive a placebo, or 100 mg of anakinra, subcutaneously, once daily. Anakinra is a human recombinant IL-1Ra, which prevents signal dunsduction of IL-1α and IL-1β (321,322). Anakinra is approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis in adults and neonatal onset multisystem inflammatory disease (323). During a 13-week treatment period, anakinra administration improved glycemia and pancreatic β-cell secretory function, compared with the placebo group. This occurred by reducing the glycated hemoglobin levels (HbA1c), the ratio of proinsulin to insulin (marker of pancreatic β-cell dysfunction and reduced insulin secretory capacity), the serum levels of systemic inflammatory markers (IL-6 and CRP), and enhanced C-peptide and insulin secretion (319) (Table II). Furthermore, Larsen *et al* (320) in a 39-week follow-up study examined the durability of anakinra administration on the management of T2DM and found maintenance of increased insulin secretion and reduction of insulin requirements (320). These findings suggest that IL-1R blockade with anakinra may improve glucose control and β-cell secretory function for a long period (319,321). Van Asseldonk *et al* (324) in a randomized, double-blind, crossover study examined the effects of anakinra in nondiabetic, obese individuals, with MetS, at a dose of 150 mg, subcutaneously, once daily for a 4-week treatment period. The authors found that anakinra administration compared with the placebo group, led to a significantly lower degree of inflammation by reducing the circulating CRP levels and the number of leukocytes accompanied by a significant increase in the disposition index and improvement in pancreatic β-cell function (324) (Table II). Nevertheless, anakinra did not significantly improve insulin sensitivity (324) (Table II). Also, van Poppel *et al* (325) assessed the effects of anakinra therapy in another double-blind, randomized, placebo-controlled crossover study, involving 16 subjects, with impaired glucose tolerance, assigned to receive 150 mg anakinra daily, for 8 weeks. A significant improvement in the first-phase insulin secretion and pancreatic β-cell function was found (325) (Table II). In line with these findings, Cucak *et al* (326) evaluated in female non-obese diabetic (NOD) mice, the effects of SER140, which is a 10-amino-acid peptide antagonist of IL-1β receptors (IL-1Ra), on the progression of diabetes and pancreatic β-cell changes. The study consisted of an 8-week treatment period. The results of this study showed a reduction in the incidence of diabetes, by >50%, compared with the control group, a decrease in non-fasting plasma glucose concentrations and an increase in plasma insulin levels. Additionally, SER140 administration changed the immune-endocrine dynamics in the NOD mouse pancreas. The authors suggested that the SER140 treatment can postpone the onset of diabetes in female NOD mice by competing with IL-1β for IL-1β receptors (IL-1R) (326).

*Treating inflammation with anti-IL-1β therapies*. Other promising IL-1β blocking therapies have demonstrated antidiabetic potential as well. Cavelti-Weder *et al* (327) evaluated the safety and biological activity of gevokizumab in patients with T2DM. Gevokizumab is a recombinant human monoclonal anti-IL-1β antibody. In this study a total of 98 patients with T2DM participated, 17 patients to the control group and 81 patients to the gevokizumab treatment group, at increasing doses. It was found that gevokizumab treatment was safe and led to significant reduction in HbA1c values (-0.85%) after 3 months, accompanied by augmented C-peptide secretion, increased insulin sensitivity and decreased CRP levels (327) (Table II). Rissanen *et al* (328) evaluated the effects of a single dose of canakinumab, a recombinant human monoclonal antibody targeting circulating IL-1β in patients with impaired glucose tolerance or T2DM treated with insulin and metformin. The authors found a trend towards increased insulin secretion (Table II). In another study conducted with 551 metformin-treated patients, with T2DM, Hensen *et al* (329)

Table II. Summary of representative experimental studies for anti-inflammatory therapies in the management of human metabolic dysfunction.

| First author/s year | Disorders | No. of participants and type of clinical Trial | Experimental drug | Mechanism | Doses | Route | Follow-up | Main effects on metabolic dysfunction | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|
| Paquot *et al* 2000 | Obesity with IR | Single-center, single blind, sequential treatment (placebo, followed by active drug) clinical trial; n=7 | Ro 45-2081: Soluble TNF-receptor p55 linked to the fc portion of human IgG1 | Recombinant TNF-α antagonist | 50 mg | IV inj. | 6 days | Ineffective in IR reduction | (347) |
| Dominguez *et al* 2005 | Obesity with T2DM | Randomized, parallel-group, open-label clinical trial; n=20 | Etanercept | Anti-TNF-α | 25 mg twice/ week | Sub-Q inj. | 4 weeks | Ineffective in IR reduction | (348) |
| Kiortsis *et al* 2005 | IR and RA or AS | n=28 with RA; n=17 with AS; clinical prospective study | Infliximab | Anti-TNF-α | 3 mg/kg at 0, 2, 6 weeks and thereafter every 8 weeks | IV inj. | 6 months | Improvement in insulin resistance | (338) |
| Bernstein *et al* 2006 | Obesity with MetS | Randomized double-blind controlled clinical trial; n=28 drug; n=28 placebo; 2 withdrew in each group. | Etanercept | Anti-TNF-α | 50 mg/week | Sub-Q inj. | 4 weeks | Reduction in inflammation markers (CRP, fibronectin); increase in total adiponectin levels; no effects on IR | (343) |
| Gonzalez-Gay *et al* 2006 | IR and RA | n=27; cohort study without placebo group due the severity of RA. | Infliximab | Anti-TNF-α | 3 or 5 mg/kg every 6 or 8 weeks according to the disease severity | IV inj. | 1 month | Improvement in IR and insulin sensitivity | (339) |
| Larsen *et al* 2007 | T2DM | n=70; randomized parallel-group, double-blind clinical trial. | Anakinra | Recombinant IL-1Ra | 10 mg/day | Sub-Q inj. | 13 weeks | Reduction in HbA1c values; reduction in pro-insulin/insulin ratio; reduction in systemic inflammatory markers (CRP, IL-6); rise in C-peptide secretion; rise in insulin secretion | (319) |
| Lo *et al* 2007 | Obesity with MetS | n=56; randomized double-blind placebo-controlled clinical trial | Etanercept | Anti-TNF-α | 50 mg/week | Sub-Q inj. | 4 weeks | Increase in total adiponectin levels; reduction in blood HMWA/total adiponectin ratio | (344) |

Table II. Continued.

| First author/s year | Disorders | No. of participants and type of clinical Trial | Experimental drug | Mechanism | Doses | Route | Follow-up | Main effects on metabolic dysfunction | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|
| Larsen *et al* 2009 | T2DM | Randomized parallel-group, double-blind trial; n=34 drug group; n=36 placebo group | Anakinra | Recombinant IL-1Ra | 10 mg/day | Sub-Q inj. | 39 weeks | Increased insulin secretion; reduction in insulin requirements | (320) |
| Ramos-Zavala *et al* 2011 | T2DM | Randomized double-blind, placebo-controlled clinical trial; n=20 drug group; n=20 placebo group | Diacerein | Anti-IL-1β in combination with TNF-α antagonism | 50 mg once or twice/day | *per os* | 2 months | Increase in insulin secretion; decrease in fasting glucose levels | (352) |
| Stanley *et al* 2011 | Obesity with MetS | Randomized placebo-controlled double blind clinical trial; n=16 drug group; n=24 placebo group | Etanercept | Anti-TNF-α | 50 mg twice/ week for the first 3 months and 50 mg/week for the final 3 months | Sub-Q inj. | 6 months | Reduction in fasting blood glucose levels; increase in blood HMWA/total adiponectin ratio | (346) |
| van Asseldonk *et al* 2011 | Obesity with MetS without T2DM | N=9; randomized, double-blind, placebo-controlled, two period crossover trial | Anakinra | Recombinant IL-1Ra | 150 mg/day | Sub-Q inj. | 4 weeks | CRP reduction values; WBC number reduction; improvement in pancreatic β-cell function; no effects on insulin sensitivity | (324) |
| Cavelti-Weder *et al* 2012 | T2DM | Randomized placebo-controlled trial; n=81 drug group (n=56 in the US arm) and (n=25 in the Swiss arm); n=17 placebo group | Gevokimumab | Anti-IL-1β | Increasing doses (0.01, 0.03, 0.1, 0.3 and 1 mg/kg) (US and Swiss arm) and 3 mg/kg | IV inj. or Sub-Q inj. | 2 months (US arm); 3 months (Swiss arm) | Reduction in HbA1c values; reduction in CRP; rise in C-peptide secretion; rise in insulin secretion; improvement in insulin sensitivity | (327) |
| Ridker *et al* 2012 | T2DM with high CV risk | n=556; randomized placebo-controlled multinational phase IIb clinical trial | Canakinumab | Anti-IL-1β | 5, 15, 50 or 150 mg/month | Sub-Q inj. | 5 months | Ineffective in HbA1c, fasting glucose and insulin values; reduction in systemic inflammatory markers (CRP, IL-6 and fibrinogen) | (330) |
| Rissanen *et al* 2012 | IGT or T2DM under insulin + metformin treatment | n=190, randomized parallel-group, placebo-controlled clinical trial | Canakinumab | Anti-IL-1β | 150 mg single dose | Sub-Q inj. | 4 weeks | Trend towards increased insulin secretion | (328) |

Table II. Continued.

| First author/s year | Disorders | No. of participants and type of clinical Trial | Experimental drug | Mechanism | Doses | Route | Follow-up | Main effects on metabolic dysfunction | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|
| Faghihimani *et al* 2013 | T2DM | Randomized, double-blind, placebo-controlled clinical trial; n=30 drug group; n=30 placebo group | Salsalate | NF-κB inhibition | 3 g/day | *per os* | 12 weeks | Reduction in HbA1c values and fasting glucose levels | (361) |
| Godfine *et al* 2013 | T2DM | Randomized placebo-controlled parallel trial; n=146 drug group; n=140 placebo group | Salsalate | NF-κB inhibition | 3.5 g/day | *per os* | 48 weeks | Reduction in HbA1c values; improvement in glycemia | (362) |
| Hensen *et al* 2013 | T2DM under Metformin treatment | Randomized, parallel-group, double-blind, placebo-controlled trial; n=372 drug group; n=179 placebo group | Canakinumab | Anti-IL-1β | 5, 15, 50 or 150 mg/month | Sub-Q inj. | 4 months | Reduction in HbA1c values; improvement in pancreatic β-cell function | (329) |
| Sloan-Lancaster *et al* 2013 | T2DM | n=106; randomized phase II, parallel-group, double-blind, placebo-controlled clinical trial | LY2189102 | Anti-IL-1β | 0.6, 18 or 180 mg/week | Sub-Q inj. | 12 weeks | Reduction in postprandial glycemic levels; reduction in inflammatory markers (CRP, IL-6) | (333) |
| Di Prospero *et al* 2014 | T2DM | Randomized double-blind, placebo-controlled study; n=41 drug group and completed trial; n=20 placebo group; n=20 pioglitazone group | JNJ-41443532 | CCR2 antagonist | 250 mg vs 1,000 mg | *per os* | 4 weeks | Reduction in HbA1c values | (357) |
| Noe *et al* 2014 | T2DM under Metfomin treatment | Randomized multicenter, double-blind, placebo-controlled, dose-escalation clinical trial; cohort 1: n=10 drug group and n=5 placebo; cohort 2: n=45 drug group; n=45 received placebo; cohort 3: n=72 drug group with different doses; n=34 placebo group; cohort 4: n=20 drug group and n=34 placebo group | Canakinumab | Anti-IL-1β | 0.03, 0.1, 0.3, 1.5 or 10 mg/kg (single dose) | IV inj. | 12 weeks | Suppression of high sensitivity CRP (hsCRP) | (332) |

Table II. Continued.

| First author/s year | Disorders | No. of participants and type of clinical Trial | Experimental drug | Mechanism | Doses | Route | Follow-up | Main effects on metabolic dysfunction | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|
| van Poppel *et al* 2014 | IGT | n=16; randomized double blind, placebo-controlled cross-over trial | Anakinra | Recombinant IL-1Ra | 150 mg/day | Sub-Q inj. | 4 weeks | Improvement in the first phase insulin secretion | (325) |
| Choudhury *et al* 2016 | ASCVD and T2DM or IGT | Randomized phase II, double-blind, placebo-controlled clinical trial; n=95 drug group; n=94 placebo group | Canakinumab | Anti-IL-1β | 150 mg/month | Sub-Q inj. | 12 months | Reduction in inflammation markers (hsCRP, IL-6) | (331) |
| Cardoso *et al* 2017 | T2DM | Randomized double-blind, placebo-controlled, parallel, clinical trial; n=43 drug group; n=41 placebo group | Diacerein | Anti-IL-1β in combination with TNF-α antagonism | 100 mg/day (single dose) | *per os* | 48 weeks | Reduction in HbA1c with peak of effect at 24 weeks of treatment | (353) |
| Piovesan *et al* 2017 | T2DM and chronic kidney disease | Randomized placebo-controlled, parallel-group trial; n=36 drug group; n=36 placebo group | Diacerein | Anti-IL-1β in combination with TNF-α antagonism | 50 mg twice/day | *per os* | 90 days | Improvement in metabolic control of T2DM; reduction in nighttime blood pressure; no effects in GFR and ACR | (356) |
| Everett *et al* 2018 | Prior MI with or without pre-diabetes or T2DM | n=10,061; randomized double-blind, placebo-controlled trial | Canakinumab | Anti-IL-1β | 50 or 150 or 300 mg every 12 weeks | Sub-Q inj. | 3.7 years | No long-term benefits in HbA1c values; No effects on the reduction of new-onset T2DM | (334) |
| Tres *et al* 2018 | T2DM | Randomized double-blind, parallel, placebo-controlled clinical trial; n=36 drug group; n=36 placebo group | Diacerein | Anti-IL-1β in combination with TNF-α antagonism | 50 mg twice/day | *per os* | 12 weeks | Reduction in HbA1c in patients with long established T2DM under long-term anti-diabetic treatment. | (354) |
| Tuttle *et al* 2018 | T2DM and diabetic kidney disease | n=129; randomized phase II, parallel-group, double blind, placebo-controlled clinical trial | Baricitinib | Anti- JAK1/ JAK2 | 0.75, 1.5 or 4 mg/day | *per os* | 24 weeks | Reduction in HbA1c values, inflammation and albuminuria | (360) |
| Genovese *et al* 2020 | RA with or without T2DM | Post hoc analysis of three randomized, controlled clinical trials; n=184 patients with T2DM; n=1,928 without diabetes. | Sarilumab vs. adalimumab | IL-6Ra vs TNF-α inhibitor | Sarilumab: 150 or 200 mg every 2 weeks vs. adalimumab: 40 mg every 2 weeks | Sub-Q inj. | Up to 24 weeks | Sarilumab was associated with more reduction in HbA1c values compared to adalimumab | (366) |

Table II. Continued.

| First author/s year | Disorders | No. of participants and type of clinical Trial | Experimental drug | Mechanism | Doses | Route | Follow-up | Main effects on metabolic dysfunction | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|
| Ruscitti *et al* 2021 | RA and T2DM | Randomized open-label, prospective, controlled, parallel-group clinical trial; n=17 received anakinra; n=15 received anti-TNFα agent for the 6-month follow-up; for the last follow-up n=15 received anakinra; n=14 anti-TNFα agent | Anakinra versus anti-TNF agents (Etanercept, Infliximab, adalimumab, golimumab, certolizumab pegol) | Recombinant IL-1Ra versus anti-TNF-α | Anakinra: 100 mg/day; Anti-TNF agents: doses according to the international guidelines | Anakinra: Sub-Q inj.; anti-TNF agents: admin-istration route according to the guidelines | 6 and 18 months | Anakinra was associated with more reduction in HbA1c values and antidiabetic drugs compared to TNF-α inhibitors at 6 months follow-up; anakinra had no effects in HbA1c values compared to TNF-α inhibitors at 18 months follow-up but continued to reduce antidiabetic drugs compared to TNF-α inhibitors | (351) |
| van den Oever *et al* 2021 | RA or OA and IR | n=36 with RA and n=33 with OA (control group) | Adalimumab | anti-TNF-α | 40mg/2weeks | Sub-Q inj. | 6 months | Improvement in IR and β-cell function in RA patients with active disease | (337) |
| Jangsripornpakorn *et al* 2022 | T2DM | Randomized, double blind, placebo-controlled trial; n=18 drug group; n=17 placebo group | Diacerein | Anti-IL-1β in combination with TNF-α antagonism | 50mg/day (single dose) | *per os* | 12 weeks | Reduction in HbA1c values | (355) |

IL-1Ra, IL-1 receptor antagonist; IL-6Ra, IL-6 receptor antagonist; SQ inj., subcutaneous injection; IV inj., intravenous injection; MI, myocardiac infraction; CCR2, C-C chemokine receptor-2 antagonist; ACR, urinary albumin/creatinine ratio; GFR, glomerular filtration rate; T2DM, type 2 diabetes mellitus; IR, insulin resistance; RA, rheumatoid arthritis; OA, osteoarthritis; ASCVD, atherosclerotic cardiovascular disease; IGT, impaired glucose tolerance; hsCRP, high sensitivity CRP; AS, ankylosing spondylitis.

assessed the safety, tolerability and effects of different monthly doses of canakinumab (5, 15, 50 or 150 mg). The authors found that canakinumab treatment was safe and well tolerated. In addition, canakinumab (50 mg) led to a reduction in HBA1c values compared with the placebo group (329) (Table II). These findings suggest that monthly adjuvant treatment, with 50 mg canakinumab, on metformin-treated patients, with T2DM, could potentially improve pancreatic β-cell function (329). However, Ridker *et al* (330) did not find alterations in HbA1c, glucose and insulin levels after canakinumab treatment in patients with T2DM with high cardiovascular risk (Table II). By contrast, cankinumab significantly reduced inflammation markers such as CRP, IL-6 and fibrinogen (330) (Table II). Choudhury *et al* (331) examined the effects of cankinumab in patients with atherosclerotic cardiovascular disease and T2DM or impaired glucose tolerance for 12 months and found reduction in inflammation markers (hsCRP, IL-6) compared with the control group (Table II). Furthermore, Noe *et al* (332) found similar results (Table II). In addition, Sloan-Lancaster *et al* (333) examined the effects of LY2189102 in the treatment of patients with T2DM. LY2189102 is a recombinant human monoclonal antibody (IgG4) that binds to IL-1β with high affinity and neutralizes its activity by forming a complex with circulating IL-1β. The authors demonstrated that the weekly subcutaneous administration of LY2189102 for 12 weeks can reduce postprandial glycemic levels and improve anti-inflammatory effects in patients with T2DM (Table II). In a canakinumab anti-inflammatory thrombosis outcomes study, IL-1β inhibition by canakinumab did not show long-term (over a median period of 3.7 years) benefits in the reduction of HbA1c values in patients prior to myocardial infarction with or without pre-diabetes or T2DM (334) (Table II). In addition, canakinumab administration was ineffective in reducing the occurrence of new onset T2DM (334) (Table II). Also, the development of vaccines against IL-1β represents a treatment option for IL-1β-dependent diseases such as T2DM (327).

*Treating inflammation with anti-TNF-α therapies*. Since obese humans have increased circulating levels of TNF-α and TNF-α levels, in human AT, is positively associated with BMI and hyperinsulinemia (317,335), their levels have been proposed to play a role in the development and pathogenesis of IR and T2DM (317,336). Indeed, van den Oever *et al* (337) in their study found that adalimumab administration in patients with RA or OA and IR improves IR and pancreatic β-cell function (337) (Table II). Adalimumab binds with specificity to TNF-α and inhibits its interaction with the p55 and p75 cell surface TNF receptors (337). Also, infliximab is a chimeric monoclonal antibody that binds TNF-α with high affinity and neutralizes TNF-α. Kiortsis *et al* (338) found that the administration of infliximab in patients with RA or ankylosing spondylitis and IR improved insulin sensitivity (Table II). Similar results were also found by Gonzalez-Gay *et al* (339) in insulin resistant patients, with RA (Table II). In addition, Haida *et al* (340) demonstrated that infliximab treatment prevents hyperglycemia and liver gluconeogenesis, in high fat diet-fed mice. Moreover, infliximab seems to ameliorate TNF-α-induced IR, in 3T3-L1 adipocytes, *in vitro,* by improving the insulin signaling pathway, via inhibition of protein tyrosine phosphatase 1B (341). Additionally, Abdelhamid *et al* (342) showed that infliximab administration in rats reduces TGs, increases HDL-c levels and reverses fructose-induced adiponectin resistance. Therefore, the authors suggested that infliximab may affect the manifestation of MetS. However, infliximab failed to affect MetS-mediated hyperglycemia, hypertension and the elevated peroxidation levels, as the levels of malondialdehyde dictate (342). Bernstein *et al* (343) investigated the effects of the inhibition of TNF-α with entanercept (a TNF-α blocker), in patients with MetS, for a 4-week treatment period. The authors concluded that etanercept reduced CRP levels (Table II). Also, Lo *et al* (344) randomized obese patients with MetS on etanercept and demonstrated increased circulating levels of total adiponectin but the ratio of high molecular weight adiponectin (HMWA) to total adiponectin was reduced (Table II); HMWA is the most biologically active form of the adipokine and is thought to mediate insulin sensitivity (345). Conversely, Stanley *et al* (346) found that the administration of etanercept, on obese individuals, with MetS, increased the ratio of HMWA to total adiponectin (Table II). Paquot *et al* (347) in their clinical trial failed to show an improvement in insulin sensitivity after TNF-α neutralization, following a single intravenous administration of a TNF receptor antagonist (Ro45-2081; a soluble TNF-receptor-IgG fusion protein) in obese insulin resistant patients (Table II). Moreover, Dominguez *et al* (348) failed to reverse vascular and metabolic IR, after short-term etanercept treatment, in obese patients with T2DM (Table II). This evidence may support the hypothesis that AT TNF-α, which is not secreted in the systemic circulation may act in an autocrine or paracrine manner. Therefore, the anti-TNF-α agents may not reach the AT microcirculation, which is markedly impaired in T2DM (347,349,350). Thus, anti-TNF-α therapy may fail to improve insulin sensitivity in such cases. In summary, treatment with anti-TNF-α agents in patients with T2DM did not yield consistent results for glucose and HbA1c reduction. Ruscitti *et al* (351) investigated the effects of anti-IL-1 treatment with anakinra compared with TNF-α inhibitors, such as etanercept, adalimumad, infliximad, certolizumab pegol or golimumab, in patients with RA and T2DM in an open label, prospective, controlled, parallel-group trial. The authors found that anakinra reduced HbA1c values compared with TNF-α inhibitors after a 6 month treatment period and also reduced antidiabetic drugs defined as the reduction of administered dosages, change from combination therapy to monotherapy or discontinuation of anti-diabetic drugs (351). However, after the mean follow-up of 18 months anakrinra had no effects in HbA1c values compared with TNF-α inhibitors but continued to reduce the use of antidiabetic drugs. On the contrary, an increase of anti-diabetic therapies was needed in participants treated with TNF-α inhibitors to reduce HbA1c levels (351) (Table II).

*Treating inflammation with synergic anti-IL-1β and anti-TNF-α therapies*. Diacerein is both an IL-1βR blocker and a TNF-α antagonist by its active metabolite, rhein (352). Ramos-Zavala *et al* (352) found that diacerein administration in patients with T2DM increased insulin secretion and decreased fasting glucose levels (Table II). In addition, Cardoso *et al* (353) found that diacerein administration reduced HbA1c values in patients with T2DM (Table II). These findings are in agreement with the studies reported from

Tres *et al* (354) (Table II) and Jangsiripornpakorn *et al* (355) (Table II). In patients with T2DM and chronic kidney disease, intervention with diacerein improves the metabolic control of T2DM and reduces nighttime blood pressure but has no effects in glomerular filtration rate and urinary albumin/creatinine ratio (356) (Table II).

*Treating inflammation with CCR2 antagonists*. Drugs targeting immune cell infiltration have been tested for anti-inflammatory and anti-obesity therapy as well. Di Prospero *et al* (357) evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of JNJ-41443532, a CCR2 antagonist, in a small sample size, double-blind, placebo-controlled, randomized, multicenter study for 4-weeks, in patients with T2DM. The authors found that JNJ-41443532 treatment was well tolerated in patients with T2DM and showed modestly improved glycemic parameters compared with the placebo group (357) (Table II). Also, Mulder *et al* (358) examined in male mice whether propagermanium, an inhibitor of CCR2, could attenuate tissue inflammation and NASH development. The results of this study showed that early propagermanium intervention was more effective than late intervention in attenuating IR, WAT inflammation and NASH development (358). In addition, Huh *et al* (359) investigated the effects of PF4178903, an antagonist for dual CCRs, CCR2 and CCR5, on obesity and IR, in high fat diet fed mice. The authors demonstrated that the dual CCR2 and CCR5 antagonist, PF4178903, attenuated metabolic dysfunction, induced by a high-fat diet. There was a decrease in body weight gain, blood glucose levels, lipid levels, adipocyte size and systemic inflammation, and an improvement in glucose tolerance and insulin sensitivity (359). Particularly, PF4178903 significantly shifted the M1 macrophage phenotype towards the M2 phenotype, in high fat diet-induced obesity, suggesting that the dual CCR2 and CCR5 blockade regulates macrophage polarization in AT macrophages (359).

*Treating inflammation with NF-κB inhibition*. Tuttle *et al* (360) found that baricitinib, an oral, reversible, selective inhibitor of JAK1 and JAK2 decreases inflammation, HBA1c and albuminuria in patients with T2DM and diabetic kidney disease. Salsalate is a product of salicylate showing anti-inflammatory effects by inhibiting the IKKb/NF-κB and JNK singnaling pathways. Faghihimani *et al* (361) found that the adiminstration of salsalate in T2DM reduced HbA1c values and fasting glucose levels (Table II). Similar results were shown in the study by Godfine *et al* (362) (Table II). Greater improvement of glycemic control of salsalate might be seen with newly diagnoseed patients with T2DM or with longer duration of antidiabetic treatment (363).

*Treating inflammation with IL-6R inhibitors*. Sarilumab is a human anti-IL-6 receptor (IL-6R) monoclonal IgG1 antibody that targets both the membrane-bound and soluble IL-6 receptor forms (364,365). Therefore, sarilumab blocks both the cis- and trans-inflammatory signaling cascades of IL-6 and reduces the activity of pro-inflammatory cytokines and inflammation (364,365). In particular, sarilumab has been shown to reduce HbA1c values after a 24 week treatment period compared with adalimumab in patients with rheumatoid arthritis with or without T2DM (366) (Table II).

*Side effects of anticytokine therapies*. However, anticytokine therapy is not devoid of unwanted side effects (367-369). Serious side effects derived from the use of anticytokines include infections, reactivation of latent tuberculosis and hepatitis B virus infection, hepatotoxicity, demyelinating disorders of the central nervous system and adverse cardiac events (369). Therefore, potential benefits should be carefully weighed against potential side effects related to the use of these medications (369).

## 7. Anti-inflammatory effects of thiazolidinediones (TZDs) in the treatment of obesity-associated T2DM

Pharmacological elevation of plasma levels of adiponectin could become a promising therapeutic strategy in countering-balacing obesity-associated T2DM (370). The thiazolidinediones (TZDs) are agonists of peroxisome proliferation activating receptor-γ (PPARγ), with TZDs such as troglitazone, rosiglitazone, glitazone and pioglitazone having been shown to increase the activation of PPARγ, elevate serum adiponectin concentrations, restore lipogenic function and decrease inflammation (371-373). TZDs also block the ability of TNF-α to inhibit insulin signaling through increased serine phosphorylation of IRS-1 (374). Wolf *et al* (375) demonstrated *in vitro* that adiponectin displays potent immunosuppressive effects inducing the production of anti-inflammatory cytokines IL-10 and IL-1Ra in myeloid cell types. In addition, IL-10 can inhibit the production of pro-inflammatory mediators by macrophages, including IL-1, IL-2, IL-6, IL-12, interferon gamma (INFγ) and TNF-α (375,376). Furthermore, adiponectin rapidly up-regulates IL-10 and subsequently increases the levels of tissue inhibitor metalloproteinase-1 (an inhibitor of matrix metalloproteinases) in human macrophages preventing the degradation of the ECM (78). Although, TZDs are effective in controlling glycemia and IR, and are not associated with hypoglycemia, when used as monotherapy (377,378), there are some serious safety concerns that must be considered when selecting TZDs for the treatment of metabolic disorders (370). For example, troglitazone was removed from the market after the FDA received reports of 94 cases of troglitazone-induced liver failure (379). Also, pioglitazone usage increases the risk of bladder cancer (380) and edema in T2DM (381,382). Another important safety issue of TZDs, is their risk for heart failure due to fluid retention (383). Moreover, glitazone has been associated with macular edema of the retina that leads to vision loss (384,385). Additionally, TZDs decrease bone density and therefore increase the bone fracture risk (386). Apart from the aforementioned side effects of TZDs, treatment with TZDs is associated with a rise in body weight due to increased fat mass and fluid retention in patients with T2DM (387,388).

## 8. Conclusion and future perspectives

Obesity has evolved to an epidemic condition that causes health impairment by increasing the risk of developing other relevant conditions, such as MetS, IR, T2DM, hypertension, atherosclerosis, dyslipidemia, CVDs, respiratory disorders and several types of cancer. The molecular and pathophysiological mechanisms linking visceral obesity and MetS are mediated by chronic low-grade inflammation and OS, but they are not fully

understood. Particularly, obesity results in a pro-inflammatory state in the adipocytes characterized by increased recruitment, accumulation and AT infiltration of M1 macrophages with a consequent release of highly pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, and pro-inflammatory adipokines, such as PAI-1, visfatin, resistin and leptin. The polarization of macrophages toward the M1 pro-inflammatory state results in reduced adiponectin levels. Accumulating evidence indicates that obesity related factors, such as a high-calorie diet, sedentary lifestyle, AT micro-environment and gut microbiota deregulation, exacerbate chronic tissue inflammation. To date, clinical studies, which tested the safety, tolerability and efficacy of molecular therapies targeting obesity-associated inflammation, have shown hopeful results by enhancing insulin sensitivity and improving metabolic function and IR, but they still remain unsatisfactory with poor treatment outcomes and in numerous cases are accompanied with serious side effects. Therefore, new efficacious and safe molecular targeted agents need to be discovered.

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FNV and PTN conceptualized the study; FNV created all the figures; FNV, MNV, VKV and PTN wrote and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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**Patient consent for publication**

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**Competing interests**

The authors declare that they have no competing interests.

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