Diabetology & Metabolic Syndrome

REVIEW

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White adipose tissue in type 2 diabetes and the effect of antidiabetic drugs

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Abstract

White adipose tissue (WAT) is highly flexible and was previously considered a passive location for energy storage. Its endocrine function has been established for several years, earning it the title of an "endocrine organ" due to its ability to secrete many adipokines that regulate metabolism. WAT is one of the core tissues that influence insulin sensitivity. Its dysfunction enhances insulin resistance and type 2 diabetes (T2D) progression. However, T2D may cause WAT dysfunction, including changes in distribution, metabolism, adipocyte hypertrophy, inflammation, aging, and adipokines and free fatty acid levels, which may exacerbate insulin resistance. This review used PubMed to search WAT dysfunction in T2D and the effects of these changes on insulin resistance. Additionally, we described and discussed the effects of antidiabetic drugs, including insulin therapy, sulfonylureas, metformin, glucose-like peptide-1 receptor agonists, thiazolidinediones, and sodium-dependent glucose transporters-2 inhibitors, on WAT parameters under T2D conditions.

Keywords Type 2 diabetes, White adipose tissue, Antidiabetic drug

Introduction

Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by decreased insulin sensitivity. Insulin normally regulates blood glucose levels within the physiological range by facilitating glucose uptake and suppressing glucose production and release by the liver. Pancreatic β cells in T2D are unable to produce sufficient insulin to counteract systemic insulin resistance causing elevated circulating blood sugar levels [1]. However, T2D is a relatively complex disease involving several pathophysiological mechanisms.

Adipose tissue is the body's largest energy storage depot. It transforms excess energy into triglycerides for storage during nutrient intake periods. It breaks down triglycerides into free fatty acids (FFAs), which provide energy for other organs, such as the liver, bones, heart muscle, pancreas, and brain, during fasting or exercise [2]. Excess FFAs cause lipid toxicity, inhibit insulin signaling, and enhance liver glucose production [3]. Therefore, proper energy storage regulation in adipose tissue is crucial for maintaining insulin sensitivity and glucose metabolism homeostasis.

White adipose tissue (WAT) accounts for > 90% of the total adipose tissue volume, and one of its most important functions is stable triglyceride storage. WAT is categorized into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). Lipids are preferentially stored in the SAT, and VAT is considered an indicator that the SAT is not storing more energy [4]. Studies across gender, age, body mass index (BMI) levels, and ethnic groups revealed that VAT plays a different and more adverse metabolic role than SAT and may be associated with an excessive increase in FFA levels and inflammatory response [5]. Additionally, WAT demonstrates the endocrine function

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and produces adipokines that impact human glucose metabolism and insulin sensitivity, including protein-like hormones secreted by adipocytes and inflammatory factors secreted by immune cells in adipose tissue, which affect glucose metabolism through different mechanisms or interactions. Previous literature suggests that pathological WAT changes due to obesity, aging, lipodystrophy, and other factors may promote insulin resistance and T2D [6–8]. However, the potential etiological role of T2D in WAT should not be neglected. Changes in T2D-induced WAT distribution and dysfunction may increase insulin resistance and speed T2D progression (Fig. 1). Herein, we focused on pathological WAT changes in T2D and their possible effects on insulin resistance, and discussed the effects of antidiabetic drugs on WAT parameters under.

WAT distribution and function

WAT is categorized into SAT and VAT based on its anatomical location. SAT is the primary location for triglyceride storage, characterized by lower lipolysis and improved lipogenic activity, thereby safeguarding insulin-sensitive tissues from lipotoxic effects [9]. However, it exhibits a limited ability to expand, according to the ability of fat cells to expand and/or recruit new cells to store excess fat. Excess triglycerides surpassing the SAT capacity are abnormally deposited in and around internal organs. More studies currently focus on epicardial adipose tissue, perirenal adipose tissue, omental adipose tissue, and intrahepatic adipose deposition. Compared to SAT, VAT demonstrates greater lipolysis activity and lower triglyceride synthesis capacity and is present in small amounts in healthy, lean individuals [4].

Research into WAT has intensified in recent years. WAT is not only recognized as an organ regulating energy homeostasis but is also considered an endocrine organ, secreting a variety of bioactive peptides and proteins, also known as adipokines. White adipocytes produce molecules, such as adiponectin, omentin-1, vaspin, visfatin, leptin, and resistin, which exhibit beneficial to detrimental effects on glucose metabolism and insulin sensitivity [10]. Additionally, under pathological conditions, white adipocytes and resident immune cells in WAT release inflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and monocyte chemoattractant protein-1 (MCP-1), which impair the insulin signaling pathway [11].

Changes in WAT distribution in T2D

We used keywords (type 2 diabetes) AND (adipose tissue) AND (distribution) to search literatures in PubMed, reviewed clinical studies, and summarized the changes

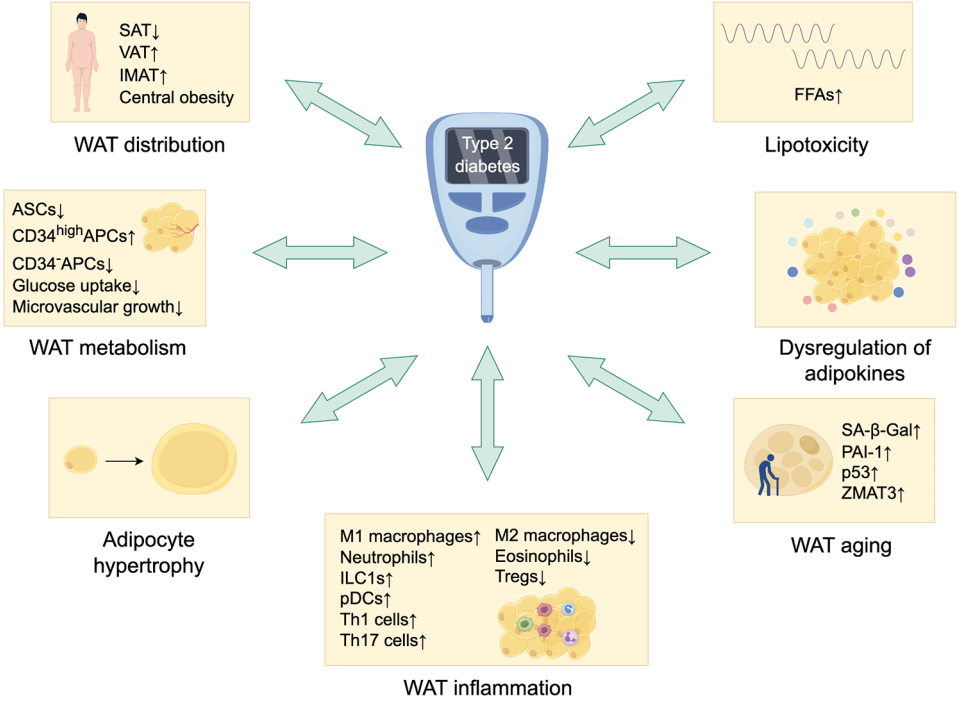

Fig. 1 Interactions between T2D and WAT. T2D causes changes in WAT distribution and metabolism, adipocyte hypertrophy, WAT inflammation, lipotoxicity, WAT aging, and dysregulation of adipokines. These pathological changes may further contribute to the progression of insulin resistance and T2D. Abbreviation: WAT: white adipose tissue; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; IMAT: intermuscular adipose tissue; ASCs: adipose tissue-derived mesenchymal stem cells; APCs: adipocyte progenitor cells; PAI-1: plasminogen activator inhibitor-1; ZMAT3: zinc finger matrin-type 3; FFAs: free fatty acids

in WAT distribution among T2D patients (S. Table S1). Patients with T2D demonstrated reduced SAT compared to healthy individuals [12–14]. This may be due to the limited expansion ability of SAT in T2D. Conversely, VAT is a more significant T2D biomarker than SAT, and it is strongly associated with glucose intolerance and insulin resistance. VAT area generally increased in patients with T2D compared to healthy subjects [14–16]. Additionally, Miyazaki et al. investigated the relationship between insulin sensitivity and fat distribution in male and female patients with T2D. They revealed that female patients with T2D demonstrated significantly higher body fat than male patients with T2D [17]. All the increase in total body fat in female patients was due to the increase in SAT area. The area of VAT was not significantly different between male and female patients. However, they demonstrated similar muscle and liver insulin resistance levels. The experimental result analysis revealed that muscle and liver insulin resistance was positively correlated with VAT area, regardless of gender.

Furthermore, a cross-sectional study revealed that obese patients with T2D exhibit higher liver and trunk fat mass but lower leg fat mass, compared to those with only obesity [18]. A similar case-control study in older participants revealed a reduced leg fat mass in patients with T2D [13]. These observations indicate that central obesity is a characteristic feature in patients with T2D. A 13-year longitudinal study emphasized higher and lower prevalence of central and peripheral obesity, respectively, in the T2D group among middle-aged black South African females in urban areas, indicating the importance of preventing central obesity to reduce T2D incidence [16].

Notably, cross-sectional studies reveal increased intermuscular adipose tissue (IMAT) in patients with T2D [14, 15]. This increase in IMAT, related to muscle mass decline, strongly correlated with insulin sensitivity, despite representing a small proportion of thigh adipose tissue [19]. Thus, these studies collectively indicate that T2D causes WAT redistribution.

WAT dysfunction in T2D

WAT metabolism

The connective tissue around mature white adipocytes contains a stromal vascular fraction, consisting of adipose tissue-derived mesenchymal stem cells (ASCs) and adipocyte progenitor cells (APCs), which are the differentiation sources of mature white adipocytes. These adipocytes, together with immune cells and blood vessels, maintain WAT stability. Mature white adipocytes renew at a rate of 8% per year; hence, the ability of ASCs and APCs to differentiate into healthy mature adipocytes is important for WAT metabolism [20].

In T2D rats, surface markers of ASCs were significantly reduced, and in vitro study has shown an increase in ASC apoptosis and a decline in their proliferation [21]. ASCs from T2D mice also exhibited decreased proliferation ability, which recovered after two or three generations of cell culture, indicating that the hyperglycemic environment caused the proliferation inhibition effect of ASCs [22]. This reduction in cell proliferation correlates with an uptick in reactive oxygen species (ROS) generation due to hyperglycemia. As pointed out by Cheng et al., treating human ASCs with the ROS inhibitor N-Acetyl-L-cysteine mitigated the high glucose-induced proliferation inhibition [23]. Cellular senescence also appears to diminish ASC proliferation. According to an in vitro study, human ASCs cultured under long-term high glucose conditions showed lower proliferative activity and increased senescence-associated β-galactosidase (SA-β-Gal) compared to those cultured under long-term low glucose conditions [24]. Another in vitro study demonstrated that high glucose can induce senescence in mesenchymal stem cells by promoting the phosphorylation of protein kinase B (AKT) and mammalian target of rapamycin [25]. Additionally, T2D causes ASCs to lose the ability to differentiate into mature and functional adipocytes. Barbagallo et al. reported the severely impaired adipogenic differentiation ability of ASCs from patients with T2D. Gene profiles of all adipogenic markers were hardly expressed in T2D ASCs after induced differentiation [26].

The healthy state of APCs is crucial for WAT function. Raajendiran et al. [27] determined three phenotypes from WAT APCs, including APCs with high, low, and no CD34 expressions. $CD34^{high}$APCs demonstrated a higher lipolysis rate than $CD34^{low}$APCs and $CD34^{-}$APCs after differentiation into mature white adipocytes. Moreover, $CD34^{high}$APCs exhibited a higher FFA uptake rate than mature white adipocytes differentiated from $CD34^{low}$APCs and $CD34^{-}$APCs, which were not strongly regulated by the anatomical location of WAT. Overall, $CD34^{high}$APC-differentiated mature white adipocytes demonstrated a significantly higher lipid turnover. The increase in $CD34^{high}$APCs and the decrease in $CD34^{-}$APCs in patients with T2D may provide a potential basis for the metabolic dysregulation of mature white adipocytes [27].

Mature white adipocytes regulate lipid turnover by synthesizing triglycerides and breaking them down through lipolysis [28]. Normally, lipid turnover is gradual, with triglycerides exhibiting a half-life ranging from 6 to 9 months [29]. Nevertheless, insulin resistance can disrupt this balance.

Allister et al. observed a marked decline in triglyceride synthesis in the SAT of individuals with insulin resistance compared to those who are insulin sensitive [30]. Furthermore, plasma FFAs measured during an insulin suppression test were 2.5-fold higher in insulin resistance subjects compared to insulin sensitive individuals

[30]. FFA esterification is dependent on insulin-mediated glucose uptake in adipocytes and the supply of glycolysis-derived glycerol-3-phosphate [31]. T2D reduces insulin-stimulated glucose uptake in WAT. The glucose uptake rate is reduced by 2–8-fold in WAT of T2D mice [32]. This may reduce the supply of glycerol-3-phosphate affecting triglyceride synthesis. Additionally, insulin is an antilipolytic hormone, and the decline of insulin sensitivity in T2D reduces its antilipolytic ability [33]. These two aspects cause the metabolic dysregulation of mature white adipocytes. Thiazolidinediones (TZDs) are hypoglycemic agents that directly act on adipose tissue. Increasing insulin-stimulated WAT glucose uptake, improving FFA esterification and antilipolytic ability of insulin are one of the effects of TZDs (troglitazone/rosiglitazone) therapy [34].

WAT needs to mediate the supply of oxygen, nutrients, hormones, stem cells, and immune cells from circulation to WAT through microvessels [35]. Incorrect microvascular growth may limit the transmission of the abovementioned factors, inhibit lipogenesis, and cause relative hypoxia and subsequent inflammatory response, thereby exacerbating metabolic dysfunction [36]. The SAT of T2D rats exhibits impaired microvascular growth ability was observed in Ferrer-Lorente et al. [21]. Improving adipose tissue angiogenesis, specifically in SAT, may contribute to the proper storage of fat and increase insulin sensitivity. Short-term treatment (6 weeks) with rosiglitazone increased capillary density and small adipocyte formation in SAT in overweight and obese individuals [37]. Moreover, T2D ASC demonstrated less vascular endothelial growth factor (VEGF) secretion [38]. Gealekman et al. investigated the mechanism whereby rosiglitazone promotes angiogenesis in WAT, finding that the VEGF system may explain why rosiglitazone promotes angiogenesis in WAT. mRNA expression of VEGFA and VEGFB was significantly increased in the adipocytes from rosiglitazone-treated animals. Furthermore, use of DMEM supplemented with purified VEGFA to culture purified microvascular endothelial cells from epididymal adipose tissue can increase capillary formation [39]. Additionally, rosiglitazone is a peroxisome proliferator-activated receptor gamma (PPARG) agonist. Angiopoietin-like factor-4 is mainly expressed in adipose tissue and a direct target of PPARG [40]. In adipocytes from rosiglitazone-treated animals, angiopoietin-like factor-4 protein expression was significantly increased. As this protein from adipocytes can stimulate endothelial cell growth and differentiation, angiopoietin-like factor-4 may be involved in the angiogenic properties of WAT promoted by rosiglitazone [39].

Adipocyte hypertrophy

Adipose tissue expansion, which begins during the second trimester of pregnancy, continues throughout life. This dynamic process occurs through two mechanisms: increasing adipocyte size and number. Sun et al. [41] described this increase in adipocyte number as healthy adipose tissue expansion, stating that it lessens inflammatory response. Conversely, pathological expansion is characterized by adipocyte hypertrophy, resulting in high-grade inflammation and extensive fibrosis. In clinical studies, white adipocytes of both patients with T2D with and without obesity demonstrated a hypertrophic phenotype [42–45], which may be associated with the decreased proliferation ability of ASCs in T2D WAT and the reduced differentiation ability into mature white adipocytes, especially in SAT. Gustafson et al. [46] revealed a decreased expression of PPARG and glucose transporter 4 (GLUT4) in the SAT of patients with T2D. Furthermore, PPARG, a key transcription factor for adipocyte differentiation, is crucial, as its genetic deletion entirely prevents adipocyte formation. A rapid loss of adipose tissue and severe insulin resistance develop in mice with adipose-specific PPARG knockout [47]. GLUT4 not only facilitates glucose uptake but also increases adipocyte differentiation [48]. Additionally, increased adipose-specific GLUT4 expression counteracts insulin resistance caused by genetic GLUT4 deletion in muscle in mice [48]. However, reduced PPARG and GLUT4 expressions impede adipocyte differentiation, thereby limiting SAT's triglyceride storage capacity. This may help increase VAT and pathological adipocyte expansion. Additionally, adipocyte hypertrophy is identified as a risk factor for T2D. Weyer et al. [49] revealed that increased adipocyte size, rather than obesity, is associated with a higher risk of T2D. Genetic susceptibility to T2D is associated with adipocyte hypertrophy caused by impaired adipocyte differentiation in SAT [50]. Henninger et al. [51] demonstrated that adipocyte hypertrophy in SAT in non-obese individuals at risk of T2D is associated with reduced insulin sensitivity, accompanied by signs of inflammation and fibrosis, in contrast to healthy subjects.

WAT inflammation

WAT inflammation is one of the important factors in developing insulin resistance and T2D. WAT contains most types of immune cells. Clinical and animal studies revealed the involvement of eosinophils, neutrophils, type 1 innate lymphoid cells (ILC1s), plasmacytoid dendritic cells (pDCs), T cells and macrophages, and ASCs in the inflammatory process underlying WAT in T2D as well as possible interactions between them (Fig. 2).

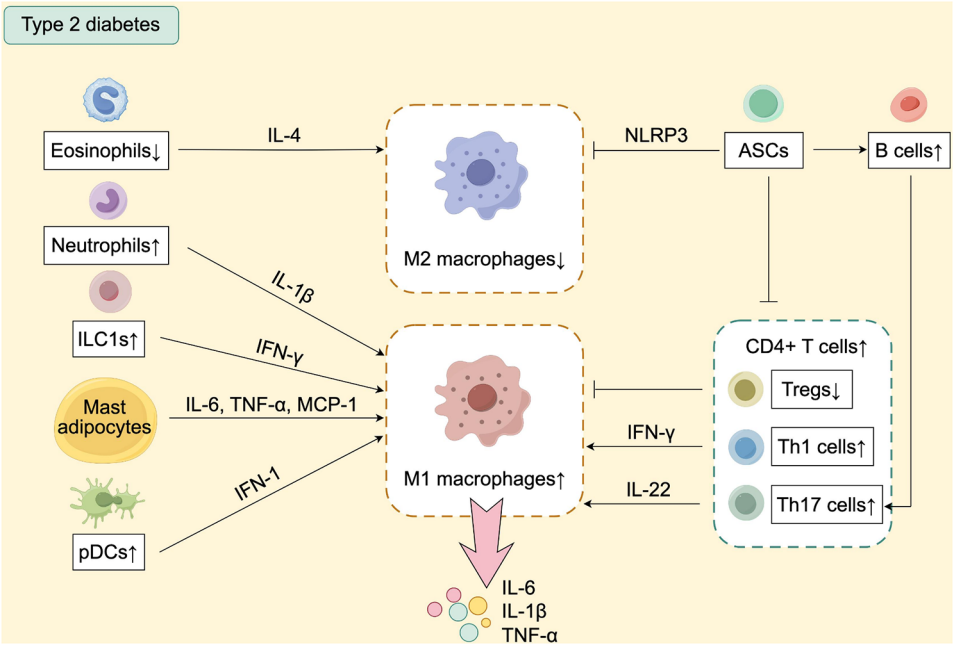

Fig. 2 WAT inflammation in T2D. In WAT affected by T2D, white adipocytes exhibit a hypertrophic phenotype and facilitate polarization of M1-type macrophages through IL-6, TNF-α, and MCP-1 secretion. Additionally, neutrophils, ILC1s, pDCs, and CD4 + T cells, including Th1 and Th17, contribute to this polarization by secreting IL-1β, IFN-γ, IFN-1, and IL-22. Conversely, eosinophils and Tregs have been shown to favor M2 macrophage polarization and suppress M1 macrophage polarization, respectively. However, presence of eosinophils and Tregs is reduced in WAT in the context of T2D. Moreover, ASCs from patients with T2D display diminished immunosuppressive capabilities, impairing their ability to support M2 macrophage polarization and restrict the proliferation of CD4 + T cells. These altered ASC functions further contribute to the enhanced proliferation of B cells, which in turn promotes an increase in Th17 cells. Abbreviation: ASCs: adipose stem cells; ILC1s: innate lymphoid cells; pDCs: plasmacytoid dendritic cells; Tregs: T regulatory lymphocytes; Th1: T helper lymphocyte 1;Th17: T helper lymphocyte 17; IL-1β: interleukin-1β; IFN-γ: interferon-γ; IFN-1: interferon-1; IL-22: interleukin-22; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6

Eosinophils

Eosinophils are innate immune system cells that are abundant in healthy WAT [52]. They mainly express IL-4 in WAT, induce M2-type macrophage polarization [53]. An Animal study revealed that increasing the number of eosinophils in WAT can enhance insulin sensitivity and glucose tolerance by promoting M2-type macrophage polarization [54]. SAT in patients with T2D contains fewer eosinophils than in those with normal glucose tolerance [55], which may be detrimental to immune homeostasis and glucose metabolism.

Neutrophils

Neutrophils are not as common in healthy WAT; moreover, their increase may have a major negative role in WAT homeostasis [56]. An intestinal metabolite, 3-hydroxydecanoate, increases with the degree of insulin resistance in obese patients with T2D [57]. A study in mice revealed that 3-hydroxydecanoate increases tissue inflammation and immune cell migration in WAT, which is associated with increased neutrophil numbers in SAT as well as neutrophils and macrophages in VAT [57]. One potential explanation for the lack of effect on macrophage recruitment to SAT may be that neutrophil recruitment precedes macrophage recruitment and VAT contains more immune cells than SAT; thus, the response to inflammation may be more obvious [55]. Studies revealed that neutrophils secrete neutrophil elastase, and neutrophil elastase reduction inhibits macrophage infiltration, which is accompanied by glucose tolerance improvement and insulin sensitivity elevation [58]. In T2D, there is not only an upsurge in lipolysis but also in FFA levels [31]. These FFAs, released during lipolysis, act upon cells expressing 5-lipoxygenase, leading to the production of leukotriene B_4, which facilitates neutrophil recruitment [59]. Interactions between neutrophils and adipocytes via the nuclear factor-κB (NF-κB) pathway result in high production of IL-1β from neutrophils and the release of chemokines like MCP-1 and MCP-3 from adipocytes, increasing macrophage infiltration and fostering M1-type polarization [59].

ILC1s

Patients with T2D demonstrated increased numbers of ILC1s in VAT [60]. Elevated levels of ILC1s in VAT may enhance adipose tissue insulin resistance by increasing the release of FFA, ultimately leading to systemic insulin resistance and subsequent hyperglycemia [60]. Additionally, an animal study revealed that ILC1s accumulation in

WAT causes interferon-γ to increase drive M1-type macrophage polarization and insulin resistance [61].

Dendritic cells

Innate and adaptive immune responses are linked through dendritic cells, as they can trigger or suppress immune responses depending on their maturity state [62]. Mature dendritic cells are categorized into two subtypes, conventional dendritic cells and pDCs. β-Catenin-secreted conventional dendritic cells increase insulin reserve to improve T2D development [63]. The number of conventional dendritic cells in SAT and epicardial adipose tissue was similar between patients with T2D compared and healthy controls. However, T2D increases the number of pDCs in SAT and epicardial adipose tissue [64]. pDCs promote a pro-inflammatory state and secrete type I interferons through MyD88-dependent signaling cascades, resulting in macrophage recruitment and M1-type polarization [65].

T cells

T cells, the backbone of adaptive immunity, are categorized into CD8 + and CD4 + subsets, and the latter can be subcategorized into T regulatory lymphocytes (Tregs) and T helper lymphocytes (Th): Th1, Th2, and Th17. WAT changes in T2D include increased Th1 and Th17 cell numbers and decreased Treg numbers. However, Th2 changes in WAT during T2D have not been sufficiently investigated thus far.

Dalmas et al. [66] revealed that CD4 + T cells increased in WAT of patients with T2D and obesity compared with those with only obesity, and CD4 + T cells interact with macrophages. Elevated blood sugar levels increase macrophage-derived IL-1β in WAT, one of the major pro-inflammatory factors secreted by M1-type macrophages. Elevated IL-1β stimulates CD4 + T cell transformation into pro-inflammatory Th17 cells and pro-inflammatory cytokines, IL-17 and IL-22, secretion. IL-22 increases IL-1β release by activating the C-Jun pathway in macrophages. Additionally, CD4 + T cell infiltration and pro-inflammatory phenomena were observed in VAT of T2D mice, indicating the increase of Th1 cells and decrease of Tregs, in addition to Th17 cell elevation [67]. Interferon-γ secreted by Th1 cells has promoted M1-type polarization of macrophages and enhanced insulin resistance [67]. The increase of Tregs in WAT reduces TNF-α and IL-1β expression and inhibits insulin resistance [68]. These indicate that T cells in WAT in T2D develop in a pro-inflammatory direction, which may further cause metabolic disorders.

Macrophages

Macrophages are key executors of downstream effects in immune response, and their polarization is categorized into classically activated (M1-type macrophage) and alternatively activated (M2-type macrophage). M1-type macrophages have a pro-inflammatory phenotype, which promotes the development of insulin resistance by secreting pro-inflammatory factors such as TNF-α, IL-1β and IL-6; however, inhibiting the polarization of M1-type macrophages in WAT can improve insulin resistance [69, 70]. M2-type macrophages are an anti-inflammatory phenotype that inhibits inflammation by secreting anti-inflammatory factors, such as IL-4 and IL-10. Furthermore, Ying el at. reported that M2-type macrophages secrete exosomes containing miRNA-690, which can improve glucose tolerance and insulin sensitivity [71]. Macrophage infiltration is less in healthy WAT, and macrophages appeared to be M2-type polarization [72]. The increase of macrophage infiltration and M1/M2 ratio indicate the transition of the WAT environment to a pro-inflammatory direction. The M1/M2 ratio in SAT and VAT in obese patients with T2D was significantly higher than that in healthy patients with obesity [73].

The size of adipocytes is a crucial determinant of macrophage infiltration and M1-type polarization, in addition to the influence of immune cells on macrophage infiltration and polarization described above. A positive correlation exists between the M1/M2 macrophage ratio and adipocyte size in abdominal SAT in patients with T2D with no obesity [43]. Adipocyte hypertrophy increases secretion of IL-6, TNF-α, and MCP-1 [11]. These pro-inflammatory factors improve macrophage infiltration into adipose tissue. Transgenic expression of MCP-1 in adipose tissue increases macrophage infiltration, inflammation, and insulin resistance. Conversely, disrupting MCP-1 hinders macrophage migration to adipose tissue, thereby diminishing inflammation and enhancing insulin sensitivity [74]. IL-6 and TNF-α production by adipocytes is crucial for macrophage accumulation in WAT and related to M1-type macrophage polarization [75].

Adipocytes trigger death when they reach a critical size [76]. Macrophages, surround dead or dying adipocytes, form a "crown-like structure," whose density positively correlates with adipocyte size [77]. Despite similar cell sizes, visceral adipocytes are more prone to death than subcutaneous ones, and thu s, contain more crown-like structures [76, 78]. The expression of M1-type macrophage markers is positive and M2-type macrophage markers are negative in these structures, indicating a pro-inflammatory state [77]. Women with obesity with T2D demonstrate a higher count of crown-like structures in both SAT and VAT compared to those with obesity with normal glucose tolerance of similar age and weight [79].

ASCs

ASCs have powerful anti-inflammatory effects and can regulate the immune system by secreting anti-inflammatory cytokines and growth factors [80], whereas T2D-derived ASCs can reduce immunosuppressive functions. Healthy receptor-derived ASCs limit the proliferation and pro-inflammatory polarization of CD4 + T cells but T2D-derived ASCs demonstrate impairment of this function [67]. Moreover, ASCs from patients with T2D markedly increase B cell proliferation [81]. Defuria et al. [82] revealed that B cells are crucial in regulating T2D inflammation due to their direct role in improving the activity of Th17 cells and secreting the pro-inflammatory cytokine IL-17. Additionally, Serena et al. [81] showed that NOD-like receptor thermal protein domain associated protein 3 signaling pathway activation in T2D ASCs reduced the effect of ASCs in inhibiting lymphocyte proliferation and activating M2-type macrophages compared with those with obesity of similar weight. This evidence indicates that T2D impairs the immunomodulatory properties of ASCs and may be detrimental to the immune balance in WAT.

WAT aging

Gustafson et al. revealed that mature adipocytes in SAT in patients with T2D exhibit a senescent phenotype, closely associated with systemic insulin resistance and adipocyte size [46]. Senescence markers, such as SA-β-Gal, plasminogen activator inhibitor-1 (PAI-1), p53, and zinc finger matrin-type 3 (ZMAT3), were markedly elevated in mature adipocytes of patients with T2D compared to those with obesity with similar body weight [46]. SA-β-Gal, a widely recognized senescence marker, exhibits activity in SAT that is sevenfold higher than in omental adipose tissue, and it correlates positively with insulin resistance indicators [83]. A significant portion of circulating PAI-1 originates from adipose tissue, with more secreting VAT than SAT [84]. Hyperglycemia stimulates PAI-1 secretion from human adipocytes in both dose- and time-dependent manners in vitro [85]. PAI-1 activates p53, which accelerates the aging process. T2D model mice indicated that elevated p53 expression in adipose tissue provokes an inflammatory response and exacerbates insulin resistance. Conversely, inhibiting p53 activity in adipose tissue greatly ameliorates age-related changes and insulin resistance [86].

T2D-induced adipocyte senescence hinders adipocyte differentiation. The deletion of the p53 inhibitor murine double minute 2 in adipocytes impairs adipogenesis, causing severe insulin resistance and glucose intolerance [87]. ZMAT3, which is highly associated with aging, is prominently expressed in first-degree relatives of patients with T2D. ZMAT3 overexpression in preadipocytes activates the p53 pathway, inhibiting adipocyte differentiation, indicating that early-life preadipocyte senescence contributes to genetic susceptibility to T2D [88]. Agareva et al. [89] revealed that T2D affects the differentiation potential of ASCs. ASCs typically differentiate into chondrogenic, osteogenic, and adipogenic lineages. However, elevated SA-β-Gal expression shifts differentiation toward osteogenesis, inhibiting adipocyte differentiation, in ASCs from patients with T2D. These results indicate that T2D-induced aging of WAT may further exacerbate insulin resistance progression.

Lipotoxicity

Lipolysis is the process by which adipocytes release FFAs. This process is regulated by the counteracting effects of catecholamines and insulin. Insulin, an antilipolytic hormone, exhibits a well-established inhibitory influence on lipolysis. The recognized mechanism involves insulin binding to its receptor on adipocyte membranes, thereby initiating tyrosine phosphorylation. Insulin receptor substrates 1 and 2 (IRS-1 and IRS-2) interaction activates the phosphatidylinositol 3-kinase (PI3K) complex. Subsequently, PI3K phosphorylates AKT and activates phosphodiesterase 3B (PDE3B), which degrades cyclic AMP, thereby diminishing protein kinase A (PKA) activity and exerting an antilipolytic effect [33, 90, 91]. Insulin resistance disrupts this balance, thereby releasing FFAs into the cytoplasm and causing their entry into circulation. Patients with T2D, with matched gender, age, and BMI with those having normal glucose tolerance, demonstrate significantly higher plasma FFA levels [92].

Notably, increased FFA levels are also implicated in the progression of T2D. FFAs from VAT directly influence the liver via the portal vein [31], enhancing gluconeogenesis through the allosteric activation of pyruvate carboxylase by acetyl-CoA [93]. Furthermore, FFAs augment glucose production by upregulating the expression of glucose-6-phosphatase in the liver.

[94]. Additionally, FFAs stimulate NADPH oxidase through protein kinase Cδ, which increases reactive oxygen species and activates the IκB kinase β (IKKβ)-c-Jun N-terminal kinase (JNK) signaling pathway, which impairs liver insulin signaling [3]. FFA uptake and oxidation rates are balanced in healthy skeletal muscle, thereby maintaining lipid intermediate equilibrium. However, elevated FFA uptake rates result in an accumulation of lipid intermediates, such as diacylglycerol, ceramide, and long-chain acyl-CoA, which hinder insulin signaling in the skeletal muscle of patients with T2D. The reduced inhibition of insulin in skeletal muscle lipolysis may increase saturated diacylglycerol accumulation, further exacerbating insulin resistance, and is partially mediated by protein kinase C [95].

Dysregulation of adipokines

T2D adversely affects the secretion of adipokines. We conducted a literature search using the keywords (type 2 diabetes) AND (adipokines) and reviewed clinical studies on PubMed. These studies indicated that levels of adiponectin, vaspin, and omentin-1 are reduced in T2D patients, whereas concentrations of leptin, chemerin, apelin, resistin, visfatin, fibroblast growth factor 21 (FGF21), and lipocalin-2 are elevated (S. Table S2) [96–105]. These adipokines are closely associated with insulin resistance and T2D (Table 1).

Adiponectin, an endogenous insulin sensitizer discovered early on, functions via its receptors, AdipoR1 and AdipoR2. AdipoR1 influences AMP-activated protein kinase (AMPK) activation, while AdipoR2 is related to peroxisome proliferator-activated receptor-α (PPAR-α) activation [133]. Both PPAR-α and AMPK signaling pathways generally promote FFA oxidation, reduce ectopic triglyceride deposition, and inhibit insulin resistance development [107, 108]. Adiponectin modulated CREB-regulated transcription coactivator 2, a key regulator of gluconeogenic enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphate catalytic subunit through the AMPK signaling pathway, which reduce hepatic gluconeogenesis [109, 110]. Adiponectin receptor agonists induce AMPK and ACC phosphorylation in the skeletal muscle, thereby stimulating glucose uptake [111]. β-cell function is impaired in adiponectin knockout mice, but it is restored by adding adiponectin [106].

Leptin reduces blood glucose levels under normal conditions. Leptin$^{-/-}$ mice demonstrate severe hyperglycemia and glucose intolerance but leptin administration rapidly normalizes glucose metabolism [134]. Leptin resistance caused by the leptin insulin feedback mechanism dysregulation, which is mainly related to leptin and insulin signaling disruption in the hypothalamus, may have elevated leptin levels in T2D. Generally, leptin downregulates forkhead box O1 (FoxO1) expression through the PI3K-AKT signaling pathway to inhibit neuronal AgRP activity to reduce food intake and improve insulin sensitivity [135]. The PI3K-AKT insulin signaling pathway is impaired in the T2D state, which reduces the inhibitory effect of leptin on FoxO1 and AgRP; thus, higher leptin levels are required to counter this leptin resistance [136, 137]. However, sustained elevated leptin levels increase the expression of suppressors of cytokine signaling 3 protein, which further enhances the development of leptin resistance and insulin resistance by inhibiting the Janus kinase (JAK)-signal transducer of activation (STAT) and PI3K-AKT signaling pathways [112]. Therefore, elevated leptin levels in T2D may be a consequence of insulin resistance and may exacerbate insulin resistance.

Vaspin aids in improving β-cell function of pancreatic islets and enhances glucose-stimulated insulin secretion [114]. Vaspin activates the IRS-PI3K-AKT-GLUT signaling pathway and inhibits the NF-κB pathway in rats on a high-fat diet, thereby improving insulin resistance in the liver, skeletal muscle, and adipose tissue [113].

Omentin-1, predominantly secreted by VAT and minimally expressed in SAT, improves insulin signaling through AKT activation in adipocytes [116]. Additionally, omentin-1 stimulates adiponectin expression [115].

Varying studies reported the role of chemerin in insulin resistance. Chemerin overexpression in mouse skeletal muscle via the AKT-forkhead box O3 (FOXO3α) signaling pathway exacerbates mitophagy-mediated insulin resistance [138]. Chemerin induces insulin resistance in human skeletal muscle cells through the IRS-1-AKT pathway and activates p38 mitogen-activated protein kinase, NF-κB, and extracellular signal-regulated kinase (ERK) 1/2, inducing insulin resistance [118]. Conversely, chemerin improves the insulin signaling pathway and glucose uptake in white adipocytes [117]. Recent studies

Table 1 Interactions between adipokines and T2D

Changes in adipokine levels in T2D	Mechanisms affecting T2D	References
Adiponectin↓	Inhibit insulin resistance; reduce hepatic gluconeogenesis; restore β-cell function	[106–111]
Leptin↑	Promote insulin resistance and leptin resistance	[112]
Vaspin↓	Improve β-cell function and enhance insulin secretion; inhibit liver, skeletal muscle and adipose tissue insulin resistance	[113, 114]
Omentin-1↓	Improve insulin signaling in adipocytes; stimulate adiponectin expression	[115, 116]
Chemerin↑	Induce insulin resistance in skeletal muscle cells; improve insulin signaling pathway in adipocytes	[117, 118]
Apelin↑	Enhance insulin sensitivity; increase β-cell mass	[119–121]
Resistin↑	Enhance hepatic gluconeogenesis; induce liver, skeletal muscle, and adipocyte insulin resistance	[122–126]
Visfatin↑	Improve insulin signaling in liver and adipose tissue; increase β-cell mass and insulin secretion; promote inflammation and insulin resistance in hepatocytes	[127–129]
FGF 21↑	Enhance insulin sensitivity; increase adiponectin levels; lower glycosylated hemoglobin levels; facilitate glucose uptake in human muscle cells	[103, 130, 131]
Lipocalin-2↑	Decrease adiponectin secretion; reduce GLUT1 and GLUT4 protein levels in adipocytes	[132]

Abbreviation: FGF21: fibroblast growth factor 21; GLUT1: glucose transporter 1; GLUT4: glucose transporter 4

revealed that chemerin knockout mice experience elevated fasting blood glucose levels and impaired glucose tolerance, thus indicating the need for further studies on chemerin's role [139].

Apelin is a bioactive peptide and exists in several active forms [140]. Study in healthy overweight males demonstrated that administration of 30 nmol/kg apelin-13 significantly enhanced insulin sensitivity [120]. In T2D rats, apelin was shown to increase pancreatic β-cell mass and decrease insulin resistance [121]. Cui et al. reported that engineered small extracellular vesicles from Wharton's jelly-derived mesenchymal stem cells loaded with apelin improved pancreatic β-cell proliferation and significantly enhanced AKT and AMPK pathway activities in WAT of T2D mice, thereby improving insulin sensitivity and glucose tolerance [119]. These studies suggest a positive role of apelin in regulating glucose metabolism. Despite these findings, clinical data and meta-analyses report increased circulating apelin levels in T2D patients [101, 141], suggesting potential apelin resistance, though the underlying mechanisms remain to be elucidated [142].

Srinivasan et al. [102] revealed significantly elevated resistin and visfatin levels in the saliva of patients with T2D. Notably, saliva is easily collected and contains approximately 50% of the serum proteome, thus it may gain clinical acceptance as a biological sample. Animal studies that use recombinant adenovirus carrying the resistant gene (ADV-resistin-EGFP) indicated that resistin inhibits liver AMPK activity, causing increased gluconeogenic enzyme expression, including PEPCK and glucose-6-phosphatase, and enhanced hepatic gluconeogenesis [125]. Resistin decreases glycogen synthase kinase 3 beta (GSK-3β) levels by inhibiting AKT activation, thereby inducing hepatic insulin resistance [126]. Resistin impairs insulin-stimulated glucose uptake by affecting IRS-1 and AKT-1 functions and reducing GLUT4 translocation in the skeletal muscle [123, 124]. Cytokine signaling 3 suppressors, which can bind to insulin receptors, are significantly upregulated by resistin in adipocytes, which increases insulin resistance [122].

Visfatin, also known as nicotinamide phosphoribosyl transferase or pro-B cell colony enhancing factor, is mainly expressed by VAT and is increased in patients with T2D [143]. A clinical study revealed that high visfatin level was positively correlated with insulin resistance [144], and several clinical studies reported no correlation between insulin resistance and visfatin level [145, 146]. At present, the exact association between visfatin level and insulin resistance is unclear. The reason for the increase in visfatin in T2D needs further investigation, and the results of relevant studies on the role of visfatin are contradictory. Visfatin overexpression improved the phosphorylation of IRS-1 in liver and adipose tissue in T2D rats [128]. Central administration of visfatin increases the β-cell mass and insulin secretion [129]. However, visfatin increases inflammation and insulin resistance through the JAK2/STAT3 and IKK/NF-κB signaling pathways in hepatocytes [127].

FGF21 is a member of the FGF superfamily, and the expression of FGF21 mRNA in human SAT is positively associated with circulating levels of FGF21 [147]. Pegbelfermin, a recombinant human FGF21 analogue, has shown potential in reducing fasting glucose levels, enhancing insulin sensitivity, and increasing adiponectin levels in obese T2D patients [148]. AKR-001, an Fc-FGF21 fusion protein, has demonstrated sustained effects on insulin sensitivity in T2D patients [130]. Treatment with an FGF21 analogue for 8 weeks in T2D mice significantly lowered glycosylated hemoglobin levels [131], while $FGF21^{-/-}$mice displayed impaired glucose tolerance [149]. In human muscle cells, FGF21 was found to increase GLUT1 surface levels, facilitating glucose uptake [103]. Although these results highlight the beneficial impact of FGF21 on glucose metabolism, clinical investigations have noted high serum FGF21 levels in T2D patients, indicating possible FGF21 resistance or an adaptive response to elevated endogenous FGF21 [103, 104].

Case-control and cross-sectional studies have found elevated serum levels of lipocalin-2 in patients with T2D [96, 105]. The case-control study, however, did not establish a correlation with glycemic control, potentially due to limited sample size [96]. Conversely, the cross-sectional study associated high lipocalin-2 levels with an increased risk of hyperglycemia [105]. Studies in lipocalin-2 knockout mice under conditions of aging or a high-fat diet showed significantly reduced fasting glucose and insulin levels and improved insulin sensitivity [150]. Kamble et al. found that recombinant human lipocalin-2 decreased adiponectin secretion and reduced GLUT1 and GLUT4 protein levels in adipocytes from both male and female SAT, suggesting that elevated lipocalin-2 may exacerbate insulin resistance in T2D [132].

Effect of antidiabetic drugs on WAT in T2D

Antidiabetic drugs may influence WAT and demonstrate beneficial effects, considering the interplay between WAT changes and insulin resistance in T2D. We reviewed the clinical studies on the effects of antidiabetic drugs on WAT in T2D, including insulin therapy, sulfonylurea, metformin (S. Table S3), glucagon-like peptide-1 receptor agonists (GLP-1RAs) (S. Table S4), TZDs (S. Table S5), and sodium-dependent glucose transporters-2 (SGLT-2) inhibitors (S. Table S6), and added several animal studies and in vitro studies as supplements. The effects of these antidiabetic drugs on WAT in T2D are summarized in Table 2.

Table 2 Effect of antidiabetic drugs on WAT in T2D

Antidiabetic drugs	Effects on WAT in T2D	References
Insulin therapy	Increase SAT; raise omentin-1and adiponectin levels	[151–153]
Sulfonylureas (glibenclamide)	Reduce FFA levels; enhance glucose transport and lipogenesis in WAT	[154, 155]
Sulfonylureas (glimepiride/glibenclamide)	Promote the hypertrophic phenotype of adipocytes; increase TNF-α mRNA expression in WAT	[156]
Metformin	Reduce VAT mass, liver fat and the levels of FFA, PAI-1 and leptin; lower serum pro-inflammatory markers (TNF-α, IL-6, IL-1β, and MCP-1) and protein levels (MCP-1, NF-κB, and NLRP3) in VAT	[157–161]
GLP-1RAs (exenatide)	Reduce liver fat and epicardial fat	[162]
GLP-1RAs (liraglutide)	Reduce VAT; increase omentin-1 levels	[163, 164]
GLP-1RAs (semaglutide)	Reduce VAT, liver steatosis and fatty liver index	[165, 166]
GLP-1RAs (tirzepatide)	Reduce liver fat content, VAT and abdominal SAT	[167]
TZDs (rosiglitazone/troglitazone)	Reduce FFA esterification, lipolysis and leptin levels; increase adiponectin levels and small adipocyte numbers	[34]
TZDs (rosiglitazone)	Reduce the intra-abdominal adipose tissue to abdominal SAT ratio, liver fat, the levels of visfatin, resistin and FFA, the expression of inflammation-related genes macrophage inflammatory protein-1α and IL-6 in SAT; increase adiponectin levels	[168–174]
TZDs (troglitazon)	Reduce VAT and intra-abdominal adipose tissue; increase SAT	[175–178]
TZDs (pioglitazone)	Reduce PAI-1 levels; increase SAT adiponectin levels	[179–181]
SGLT-2 inhibitors (canagliflozin)	Reduce VAT	[182]
SGLT-2 inhibitors (Dapagliflozin)	Reduce liver fat, adipose tissue volume, body fat mass, and abdominal VAT and SAT; increase adiponectin levels	[183–185]
SGLT-2 inhibitors (empagliflozin)	Reduce VAT and liver fat; decrease the expression of pro-inflammatory cytokines and diminishing macrophage infiltration in VAT	[186, 187]

Abbreviation: SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; FFA: free fatty acid; PAI-1: plasminogen activator inhibitor-1; TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; IL-6: interleukin-6; MCP-1: monocyte chemoattractant protein-1; NF-κB: nuclear factor-kappa B; NLRP3: NOD-like receptor thermal protein domain associated protein 3

Insulin therapy

Insulin therapy, a direct approach to controlling blood glucose, frequently causes weight gain, as it promotes fat synthesis. In a randomized, placebo-controlled trial, obese patients with T2D were randomly assigned to intensive insulin therapy alone or combined with pioglitazone for 12–16 weeks. The study revealed no significant change in VAT, with both treatment groups experiencing weight and SAT gains after treatment, particularly in the insulin plus pioglitazone group [152]. Another clinical study explored the effects of a twice-daily administered biphasic insulin mixture 70/30, which enhanced omentin-1 expression over 6 months [153]. Moreover, insulin therapy was found to elevate body weight and total fat mass in T2D rats, with a greater accumulation in SAT compared to VAT, and raised serum adiponectin levels [151]. These findings suggest that insulin treatment, despite the associated weight gain, may cause a healthier WAT distribution and positively affect adipokines.

Sulfonylureas

Sulfonylureas mainly stimulate pancreatic islets β-cells to secrete insulin to reduce blood glucose. Studies on their effects on WAT in T2D are very limited. A 13-week clinical study revealed that sulfonylurea treatment failed to reduce plasma FFA levels in patients with T2D, and the specific drugs used were not described [155]. A prospective study revealed that glimepiride at 0.5–1 mg/day for 28 weeks did not reduce VAT area in patients with T2D [188]. In another clinical study, the initial dose of glibenclamide treatment was 1.75 mg and gradually increased until the fasting blood glucose reached ~ 7.0 mmol/L or total daily dose reached 7 mg for 3 months, this treatment enhanced insulin-stimulated glucose transport and lipogenesis in WAT in moderately obese patients with T2D [154]. However, glimepiride and glibenclamide treatment promoted the hypertrophic phenotype of adipocytes and increased TNF-α mRNA expression in WAT, especially glibenclamide, in obese T2D rats [156]. Therefore, the effect of sulfonylureas on WAT should be carefully considered.

Metformin

Metformin is the most widely prescribed drug for T2D treatment, with a strong hypoglycemic effect and recognized safety. It has positive effects on WAT under T2D conditions. In a randomized double-blind placebo-controlled trial, administering metformin at a dosage of 1 g twice daily for 26 weeks reduced body weight and VAT mass in patients with T2D [158]. A prospective study assessed the impact of metformin, administered at 1 g twice daily for 4 months, noting a reduction in liver fat but not in overall body weight in newly diagnosed T2D patients [159]. Moreover, a transversal study in obese

patients with T2D revealed that metformin treatment diminished the activation of the NOD-like receptor thermal protein domain associated protein 3 inflammasome complex in VAT and associated pro-inflammatory factors TNF-α, IL-6, IL-1β and MCP-1, indicating metformin's inhibitory effect on WAT inflammation [160]. A single-center, double-masked, double-dummy, cross-over study reported that metformin administered at 1 g twice daily for 4 months reduced FFA levels in patients with T2D [161]. An in vitro study revealed that metformin inhibited catecholamine-stimulated lipolysis through decreased PKA activity by reducing cyclic AMP production and lessening phosphorylation of perilipin and lipase activity. Perilipin coats the lipid droplet surface, serving as a barrier to protect triglycerides from hydrolysis by lipases. PKA phosphorylation disrupts perilipin's barrier function, initiating lipolytic activity [189]. Additionally, a clinical study reported that metformin lowered PAI-1 and leptin levels in patients with T2D without affecting adiponectin levels [157]. In T2D rats, metformin was found to increase AdipoR1 and AdipoR2 expression in WAT, which may enhance adiponectin's role in improving insulin sensitivity [190].

GLP-1RAs

GLP-1RAs improve glucose-dependent insulin secretion triggered by food intake by stimulating GLP-1 secretion, inhibiting inappropriate glucagon secretion, slowing gastric emptying, and significantly reducing body weight [191]. A systematic review and meta-analysis revealed that GLP-1 receptor agonist treatment in patients with T2D reduced both VAT and SAT, with VAT demonstrating a greater decrease. Especially, exenatide and liraglutide had a positive effect on fat distribution [192]. In a prospective randomized study, the administration of exenatide at 5 ug twice daily for 4 weeks, followed by 10 ug for the next 22 weeks, led to significant reductions in liver and epicardial fat content among obese T2D patients [162]. A placebo-controlled trial revealed that liraglutide injections of 1.8 mg/day significantly reduced VAT in South Asian patients with T2D, with VAT reduction correlating with a decrease in HbA1c levels [164]. A cross-sectional study reported that on the background of metformin treatment, patients with T2D treated with 1.2 mg of liraglutide daily for 16 weeks experienced a significant increase in plasma omentin-1 [163].

Furthermore, a prospective study revealed that adding semaglutide to metformin treatment, starting with a weekly subcutaneous injection of 0.25 mg for one month, then increasing to 0.5 mg, and further to 1 mg after six months, significantly reduced VAT and liver steatosis in patients with T2D after 52 weeks [166]. Another prospective study revealed that oral administration of semaglutide at 3 mg/day, increased to 7 mg/day after 30 days, demonstrated similar effects, significantly reducing the fatty liver index and visceral fat after 26 weeks of treatment [165]. Tirzepatide, a new GLP-1RA under development, administered weekly at doses of 5 mg, 10 mg, or 15 mg, significantly reduced liver fat content, VAT, and abdominal SAT in patients with T2D after 52 weeks of treatment [167].

TZDs

TZDs are usually used in combination with diet, metformin, or sulfonylurea to improve glycemic control and are associated with significant weight gain. TZDs belong to PPARG agonists. PPARG is highly expressed in WAT and much lower in the liver and skeletal muscle [193]. This indicates that WAT is an important direct target tissue of TZDs. A cross-over, placebo-controlled study revealed that TZDs improved the inhibitory effect of insulin on lipolysis and FFA esterification, and increased the number of small and medium-sized adipocytes in SAT. Moreover, TZDs increased plasma adiponectin levels and decreased leptin levels. Although the therapeutic drugs used by the 8 subjects included in this study were slightly different, 5 used rosiglitazone of 8 mg/day and the other 3 used troglitazone of 600 mg/day, this study indicated that TZDs have positive effects on WAT under T2D conditions [34].

In Korean patients with T2D, administration of rosiglitazone at a dose of 4 mg/day, increased to 8 mg/day after 6 months, reduced the intra-abdominal adipose tissue to abdominal SAT ratio after 12 months [169]. In a double-blind randomized study, rosiglitazone treatment (8 mg/day) for 16 weeks reduced liver fat and increased adiponectin levels in patients with T2D [170]. Several other clinical studies revealed that rosiglitazone regulated the expression of adipokines in T2D patients, not only the increase of adiponectin levels but also the decrease of visfatin and resistin levels [171–173]. Kolak et al. revealed that rosiglitazone increased the expression of genes involved in triacylglycerol storage, such as stearyl-CoA desaturase and CD36, and reduced the expression of inflammation-related genes macrophage inflammatory protein-1α and IL-6 in SAT of T2D patients [168]. Tan et al. emphasized the role of rosiglitazone in reducing postprandial FFA concentration in obese patients with T2D, mainly related to improving postprandial insulin sensitivity-related antilipolytic ability [174]. Similarly, in T2D rats, rosiglitazone was found to induce the expression of PCK1 in WAT, thereby promoting triglyceride production, and it inhibited lipolysis, leading to a reduction in FFA levels [194].

Troglitazone is contraindicated due to liver toxicity, but early clinical studies on its effect on WAT also deserve attention. A clinical study investigated the combination of a troglitazone treatment of 400 mg/day with diet or

sulfonylurea over 3 months in T2D patients, and revealed that both 2 groups reduced VAT, with a slight weight gain associated with increased SAT [176]. Another clinical study reached the same conclusion in T2D patients treated with troglitazone 400 mg/day with diet for 6 months [177]. Akazawa et al. reported that troglitazone 400 mg/day for one year caused weight gain and an increase in SAT, but no change in VAT in patients with T2D inadequately controlled with diet, sulfonylurea, and other drugs [178]. In a Double-blind randomized study, troglitazone treatment of 600 mg/d for 12 weeks alone reduced intra-abdominal adipose tissue without affecting total body fat or body weight in obese patients with T2D [175]. These indicated the positive effect of troglitazone on WAT distribution in T2D.

A clinical study revealed that pioglitazone 30 mg/day in addition to diet or sulfonylureas increased body weight, SAT, and adiponectin levels in patients with T2D [180]. Obese patients with T2D inadequately controlled with metformin and sulfonylureas demonstrated that 24 weeks of pioglitazone combination treatment at 30 mg/day increased SAT without affecting intra-abdominal adipose tissue [181]. In a randomized, double-blind, placebo-controlled, mechanistic study, metformin and sulfonylureas combined with pioglitazone of 15 mg/day for 6 months reduced PAI-1 levels and increased adiponectin levels in obese patients with T2D [179]. These evidences indicate that the beneficial effect of pioglitazone on WAT is related to increasing SAT and adiponectin levels and reducing PAI-1 levels.

SGLT-2 inhibitors

SGLT-2 inhibitors promote glucose excretion in the urine by blocking glucose reabsorption in the kidneys with a daily energy loss of ~ 300 kcal and may therefore contribute to weight loss [195]. Several clinical studies revealed the beneficial effects of SGLT-2 inhibitors on WAT. Compared with metformin, canagliflozin of 100 mg/day for 12 weeks significantly reduced VAT in patients with T2D [182]. In a randomized, double-blind, placebo-controlled, cross-over study, once-daily administration of 10 mg dapagliflozin for 12 weeks significantly reduced liver fat although the VAT/SAT ratio remained unchanged [184]. Combining dapagliflozin with other therapies may improve its beneficial impact on fat distribution. Dapagliflozin of 10 mg/day plus saxagliptin of 5 mg/day in patients with T2D on metformin of ≥ 1500 mg/day diminished liver fat and total fat mass [185]. Moreover, another clinical study revealed that in T2D patients with poorly controlled metformin, a daily dose of 10 mg of dagliprazin reduced body fat mass, abdominal VAT and SAT, while increasing adiponectin levels [183]. Empagliflozin administered at 10 mg/day for 12 weeks in patients with T2D markedly decreased VAT and liver fat content [187]. Additionally, empagliflozin has been observed to reduce the expression of pro-inflammatory cytokines, including MCP-1, TNF-α, IL-1β, IL-6, and IL-10 as well as diminishing macrophage infiltration in VAT of T2D rats, highlighting its anti-inflammatory properties [186].

Conclusion

WAT is a metabolic tissue with considerable plasticity and stands as one of the core tissues linked to insulin sensitivity. Its dysfunction can exacerbate insulin resistance and the progression of T2D. We reviewed the changes of WAT in T2D in PubMed, including changes in distribution, metabolism, adipocyte hypertrophy, inflammation, aging, adipokines, and FFA levels, all of which may exacerbate insulin resistance. Notably, pathological changes in WAT do not only result from T2D but are also a contributor. Furthermore, we evaluated the influence of antidiabetic medications on these WAT changes, primarily based on clinical study data. Treatments such as insulin therapy and TZDs often lead to increased body weight and fat mass, yet may have beneficial impacts on WAT distribution, adipokine changes, or FFA levels. Conversely, drugs like sulfonylureas have shown minimal effect on WAT characteristics, occasionally even exhibiting detrimental outcomes. GLP-1RAs have been found to help reduce VAT mass. Metformin and SGLT-2 inhibitors appear to improve WAT distribution, enhance adipokine release, and curb WAT inflammation. Given WAT's significant endocrine functions, the current research on the metabolic impacts of these antidiabetic drugs remains inadequate. There is also a scarcity of detailed mechanistic insights from animal or in vitro studies into how these drugs modify WAT, particularly concerning their effects on various inflammatory cells within WAT, adipocyte senescence, and adipocyte metabolism. Investigating antidiabetic medications can enhance our understanding of WAT's role in T2D. Therefore, further clinical and preclinical research is warranted.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

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Declarations

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References

1. Christensen AA, Gannon M. The beta cell in type 2 diabetes. Curr Diab Rep. 2019;19:81. https://doi.org/10.1007/s11892-019-1196-4.
2. Saely CH, Geiger K, Drexel H. Brown versus white adipose tissue: a mini-review. Gerontology. 2012;58:15–23. https://doi.org/10.1159/000321319.
3. Pereira S, Park E, Mori Y, Haber CA, Han P, Uchida T, et al. FFA-induced hepatic insulin resistance in vivo is mediated by PKCδ, NADPH oxidase, and oxidative stress. Am J Physiol Endocrinol Metab. 2014;307:E34–46. https://doi.org/10.1152/ajpendo.00436.2013.
4. Bódis K, Roden M. Energy metabolism of white adipose tissue and insulin resistance in humans. Eur J Clin Invest. 2018;48:e13017. https://doi.org/10.1111/eci.13017.
5. Tchernof A, Després J-P. Pathophysiology of human visceral obesity: an update. Physiol Rev. 2013;93:359–404. https://doi.org/10.1152/physrev.00033.2011.
6. Knebel B, Müller-Wieland D, Kotzka J. Lipodystrophies-Disorders of the fatty tissue. Int J Mol Sci. 2020;21:8778. https://doi.org/10.3390/ijms21228778.
7. Zatterale F, Longo M, Naderi J, Raciti GA, Desiderio A, Miele C, et al. Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. Front Physiol. 2019;10:1607. https://doi.org/10.3389/fphys.2019.01607.
8. Zhao Y, Yue R. Aging adipose tissue, insulin resistance, and type 2 diabetes. Biogerontology. 2024;25:53–69. https://doi.org/10.1007/s10522-023-10067-6.
9. Patel P, Abate N. Role of subcutaneous adipose tissue in the pathogenesis of insulin resistance. J Obes. 2013;2013:489187. https://doi.org/10.1155/2013/489187.
10. Pittas AG, Joseph NA, Greenberg AS. Adipocytokines and insulin resistance. J Clin Endocrinol Metab. 2004;89:447–52. https://doi.org/10.1210/jc.2003-031005.
11. Skurk T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. J Clin Endocrinol Metab. 2007;92:1023–33. https://doi.org/10.1210/jc.2006-1055.
12. Bozzetto L, Prinster A, Mancini M, Giacco R, De Natale C, Salvatore M, et al. Liver fat in obesity: role of type 2 diabetes mellitus and adipose tissue distribution. Eur J Clin Invest. 2011;41:39–44. https://doi.org/10.1111/j.1365-2362.2010.02372.x.
13. Bell KE, Paris MT, Avrutin E, Mourtzakis M. Altered features of body composition in older adults with type 2 diabetes and prediabetes compared with matched controls. J Cachexia Sarcopenia Muscle. 2022;13:1087–99. https://doi.org/10.1002/jcsm.12957.
14. Gallagher D, Kelley DE, Yim J-E, Spence N, Albu J, Boxt L, et al. Adipose tissue distribution is different in type 2 diabetes. Am J Clin Nutr. 2009;89:807–14. https://doi.org/10.3945/ajcn.2008.26955.
15. Goodpaster BH, Krishnaswami S, Resnick H, Kelley DE, Haggerty C, Harris TB, et al. Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. Diabetes Care. 2003;26:372–9. https://doi.org/10.2337/diacare.26.2.372.
16. Mtintsilana A, Micklesfield LK, Chorell E, Olsson T, Goedecke JH. Fat redistribution and accumulation of visceral adipose tissue predicts type 2 diabetes risk in middle-aged black South African women: a 13-year longitudinal study. Nutr Diabetes. 2019;9:12. https://doi.org/10.1038/s41387-019-0079-8.
17. Miyazaki Y, Glass L, Triplitt C, Wajcberg E, Mandarino LJ, DeFronzo RA. Abdominal fat distribution and peripheral and hepatic insulin resistance in type 2 diabetes mellitus. Am J Physiol Endocrinol Metab. 2002;283:E1135–1143. https://doi.org/10.1152/ajpendo.0327.2001.
18. Azuma K, Heilbronn LK, Albu JB, Smith SR, Ravussin E, Kelley DE, et al. Adipose tissue distribution in relation to insulin resistance in type 2 diabetes mellitus. Am J Physiol Endocrinol Metab. 2007;293:E435–442. https://doi.org/10.1152/ajpendo.00394.2006.
19. Goodpaster BH, Thaete FL, Kelley DE. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. Am J Clin Nutr. 2000;71:885–92. https://doi.org/10.1093/ajcn/71.4.885.
20. Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, et al. Dynamics of fat cell turnover in humans. Nature. 2008;453:783–7. https://doi.org/10.1038/nature06902.
21. Ferrer-Lorente R, Bejar MT, Tous M, Vilahur G, Badimon L. Systems biology approach to identify alterations in the stem cell reservoir of subcutaneous adipose tissue in a rat model of diabetes: effects on differentiation potential and function. Diabetologia. 2014;57:246–56. https://doi.org/10.1007/s00125-013-3081-z.
22. Wang M, Song L, Strange C, Dong X, Wang H. Therapeutic effects of adipose stem cells from diabetic mice for the treatment of type 2 diabetes. Mol Ther. 2018;26:1921–30. https://doi.org/10.1016/j.ymthe.2018.06.013.
23. Cheng N-C, Hsieh T-Y, Lai H-S, Young T-H. High glucose-induced reactive oxygen species generation promotes stemness in human adipose-derived stem cells. Cytotherapy. 2016;18:371–83. https://doi.org/10.1016/j.jcyt.2015.11.012.
24. Li C-W, Young T-H, Wang M-H, Pei M-Y, Hsieh T-Y, Hsu C-L, et al. Low-glucose culture environment can enhance the wound healing capability of diabetic adipose-derived stem cells. Stem Cell Res Ther. 2023;14:236. https://doi.org/10.1186/s13287-023-03478-2.
25. Zhang D, Lu H, Chen Z, Wang Y, Lin J, Xu S, et al. High glucose induces the aging of mesenchymal stem cells via Akt/mTOR signaling. Mol Med Rep. 2017;16:1685–90. https://doi.org/10.3892/mmr.2017.6832.
26. Barbagallo I, Li Volti G, Galvano F, Tettamanti G, Pluchinotta FR, Bergante S, et al. Diabetic human adipose tissue-derived mesenchymal stem cells fail to differentiate in functional adipocytes. Exp Biol Med (Maywood). 2017;242:1079–85. https://doi.org/10.1177/1535370216681552.
27. Raajendiran A, Ooi G, Bayliss J, O'Brien PE, Schittenhelm RB, Clark AK, et al. Identification of metabolically distinct adipocyte progenitor cells in human adipose tissues. Cell Rep. 2019;27:1528–e15407. https://doi.org/10.1016/j.celrep.2019.04.010.
28. Palacios-Marin I, Serra D, Jimenez-Chillarón J, Herrero L, Todorčević M. Adipose tissue dynamics: cellular and lipid turnover in health and disease. Nutrients. 2023;15:3968. https://doi.org/10.3390/nu15183968.
29. Strawford A, Antelo F, Christiansen M, Hellerstein MK. Adipose tissue triglyceride turnover, de Novo lipogenesis, and cell proliferation in humans measured with 2H2O. Am J Physiol Endocrinol Metab. 2004;286:E577–588. https://doi.org/10.1152/ajpendo.00093.2003.
30. Allister CA, Liu L, Lamendola CA, Craig CM, Cushman SW, Hellerstein MK, et al. In vivo 2H2O administration reveals impaired triglyceride storage in adipose tissue of insulin-resistant humans. J Lipid Res. 2015;56:435. https://doi.org/10.1194/jlr.M052860.
31. Prentki M, Madiraju SRM. Glycerolipid/free fatty acid cycle and islet β-cell function in health, obesity and diabetes. Mol Cell Endocrinol. 2012;353:88–100. https://doi.org/10.1016/j.mce.2011.11.004.
32. Makarova E, Makrecka-Kuka M, Vilks K, Volska K, Sevostjanovs E, Grinberga S, et al. Decreases in Circulating concentrations of Long-Chain acylcarnitines and free fatty acids during the glucose tolerance test represent Tissue-Specific insulin sensitivity. Front Endocrinol (Lausanne). 2019;10:870. https://doi.org/10.3389/fendo.2019.00870.
33. Protein. accessed January 2, kinase B activity is required for the effects of insulin on lipid metabolism in adipocytes - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/19158325/ (2024).

34. Boden G, Cheung P, Mozzoli M, Fried SK. Effect of Thiazolidinediones on glucose and fatty acid metabolism in patients with type 2 diabetes. Metabolism. 2003;52:753–9. https://doi.org/10.1016/S0026-0495(03)00055-6.
35. Mannerås-Holm L, Krook A. Targeting adipose tissue angiogenesis to enhance insulin sensitivity. Diabetologia. 2012;55:2562–4. https://doi.org/10.1007/s00125-012-2651-9.
36. Gealekman O, Guseva N, Hartigan C, Apotheker S, Gorgoglione M, Gurav K, et al. Depot specific differences and insufficient subcutaneous adipose tissue angiogenesis in human obesity. Circulation. 2011;123:186–94. https://doi.org/10.1161/CIRCULATIONAHA.110.970145.
37. Gealekman O, Guseva N, Gurav K, Gusev A, Hartigan C, Thompson M, et al. Effect of Rosiglitazone on capillary density and angiogenesis in adipose tissue of normoglycaemic humans in a randomised controlled trial. Diabetologia. 2012;55:2794–9. https://doi.org/10.1007/s00125-012-2658-2.
38. Sun Y, Song L, Zhang Y, Wang H, Dong X. Adipose stem cells from type 2 diabetic mice exhibit therapeutic potential in wound healing. Stem Cell Res Ther. 2020;11:298. https://doi.org/10.1186/s13287-020-01817-1.
39. Gealekman O, Burkart A, Chouinard M, Nicoloro SM, Straubhaar J, Corvera S. Enhanced angiogenesis in obesity and in response to PPARγ activators through adipocyte VEGF and ANGPTL4 production. Am J Physiol Endocrinol Metab. 2008;295:E1056–64. https://doi.org/10.1152/ajpendo.90345.2008.
40. Kersten S, Mandard S, Tan NS, Escher P, Metzger D, Chambon P, et al. Characterization of the fasting-induced adipose factor FIAF, a novel peroxisome proliferator-activated receptor target gene. J Biol Chem. 2000;275:28488–93. https://doi.org/10.1074/jbc.M004029200.
41. Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. J Clin Invest. 2011;121:2094–101. https://doi.org/10.1172/JCI45887.
42. Liu F, He J, Liu B, Zhang P, Wang H, Sun X, et al. Association of omental adipocyte hypertrophy and fibrosis with human obesity and type 2 diabetes. Obes (Silver Spring). 2021;29:976–84. https://doi.org/10.1002/oby.23155.
43. Acosta JR, Douagi I, Andersson DP, Bäckdahl J, Rydén M, Arner P, et al. Increased fat cell size: a major phenotype of subcutaneous white adipose tissue in non-obese individuals with type 2 diabetes. Diabetologia. 2016;59:560–70. https://doi.org/10.1007/s00125-015-3810-6.
44. Rydén M, Andersson DP, Bergström IB, Arner P. Adipose tissue and metabolic alterations: regional differences in fat cell size and number matter, but differently: a cross-sectional study. J Clin Endocrinol Metab. 2014;99:E1870–1876. https://doi.org/10.1210/jc.2014-1526.
45. Pourdashti S, Faridi N, Monem-Homaie F, Yaghooti SH, Soroush A, Bathaie SZ. The size of human subcutaneous adipocytes, but not adiposity, is associated with inflammation, Endoplasmic reticulum stress, and insulin resistance markers. Mol Biol Rep. 2023;50:5755–65. https://doi.org/10.1007/s11033-023-08460-y.
46. Gustafson B, Nerstedt A, Spinelli R, Beguinot F, Smith U. Type 2 diabetes, independent of obesity and age, is characterized by senescent and dysfunctional mature human adipose cells. Diabetes. 2022;71:2372–83. https://doi.org/10.2337/db22-0003.
47. Wang F, Mullican SE, DiSpirito JR, Peed LC, Lazar MA. Lipoatrophy and severe metabolic disturbance in mice with fat-specific deletion of PPARγ. Proc Natl Acad Sci U S A. 2013;110:18656–61. https://doi.org/10.1073/pnas.1314863110.
48. Carvalho E, Kotani K, Peroni OD, Kahn BB. Adipose-specific overexpression of GLUT4 reverses insulin resistance and diabetes in mice lacking GLUT4 selectively in muscle. Am J Physiol Endocrinol Metab. 2005;289:E551–561. https://doi.org/10.1152/ajpendo.00116.2005.
49. Weyer C, Foley JE, Bogardus C, Tataranni PA, Pratley RE. Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts type II diabetes independent of insulin resistance. Diabetologia. 2000;43:1498–506. https://doi.org/10.1007/s001250051560.
50. Arner P, Arner E, Hammarstedt A, Smith U. Genetic predisposition for type 2 diabetes, but not for overweight/obesity, is associated with a restricted adipogenesis. PLoS ONE. 2011;6:e18284. https://doi.org/10.1371/journal.pone.0018284.
51. Henninger AMJ, Eliasson B, Jenndahl LE, Hammarstedt A. Adipocyte hypertrophy, inflammation and fibrosis characterize subcutaneous adipose tissue of healthy, non-obese subjects predisposed to type 2 diabetes. PLoS ONE. 2014;9:e105262. https://doi.org/10.1371/journal.pone.0105262.
52. Kane H, Lynch L. Innate immune control of adipose tissue homeostasis. Trends Immunol. 2019;40:857–72. https://doi.org/10.1016/j.it.2019.07.006.
53. Wu D, Molofsky AB, Liang H-E, Ricardo-Gonzalez RR, Jouihan HA, Bando JK, et al. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. Science. 2011;332:243–7. https://doi.org/10.1126/science.1201475.
54. Hussaarts L, García-Tardón N, van Beek L, Heemskerk MM, Haeberlein S, van der Zon GC, et al. Chronic helminth infection and helminth-derived egg antigens promote adipose tissue M2 macrophages and improve insulin sensitivity in obese mice. FASEB J. 2015;29:3027–39. https://doi.org/10.1096/fj.14-266239.
55. Lenz M, Arts ICW, Peeters RLM, de Kok TM, Ertaylan G. Adipose tissue in health and disease through the lens of its Building blocks. Sci Rep. 2020;10:10433. https://doi.org/10.1038/s41598-020-67177-1.
56. Talukdar S, Oh DY, Bandyopadhyay G, Li D, Xu J, McNelis J, et al. Neutrophils mediate insulin resistance in mice fed a high-fat diet through secreted elastase. Nat Med. 2012;18:1407–12. https://doi.org/10.1038/nm.2885.
57. Mikkelsen RB, Arora T, Trošt K, Dmytriyeva O, Jensen SK, Meijnikman AS, et al. Type 2 diabetes is associated with increased Circulating levels of 3-hydroxydecanoate activating GPR84 and neutrophil migration. iScience. 2022;25:105683. https://doi.org/10.1016/j.isci.2022.105683.
58. Talukdar S, Oh DY, Bandyopadhyay G, Li D, Xu J, McNelis J, et al. Neutrophils mediate insulin resistance in high fat diet fed mice via secreted elastase. Nat Med. 2012;18:1407–12. https://doi.org/10.1038/nm.2885.
59. Watanabe Y, Nagai Y, Honda H, Okamoto N, Yanagibashi T, Ogasawara M, et al. Bidirectional crosstalk between neutrophils and adipocytes promotes adipose tissue inflammation. FASEB J. 2019;33:11821–35. https://doi.org/10.1096/fj.201900477RR.
60. Liu F, Wang H, Feng W, Ye X, Sun X, Jiang C, et al. Type 1 innate lymphoid cells are associated with type 2 diabetes. Diabetes Metab. 2019;45:341–6. https://doi.org/10.1016/j.diabet.2018.08.005.
61. O'Sullivan TE, Rapp M, Fan X, Weizman O-E, Bhardwaj P, Adams NM, et al. Adipose-Resident group 1 innate lymphoid cells promote Obesity-Associated insulin resistance. Immunity. 2016;45:428–41. https://doi.org/10.1016/j.immuni.2016.06.016.
62. Joffre OP, Segura E, Savina A, Amigorena S. Cross-presentation by dendritic cells. Nat Rev Immunol. 2012;12:557–69. https://doi.org/10.1038/nri3254.
63. Macdougall CE, Wood EG, Solomou A, Scagliotti V, Taketo MM, Gaston-Massuet C, et al. Constitutive activation of β-Catenin in conventional dendritic cells increases the insulin reserve to ameliorate the development of type 2 diabetes in mice. Diabetes. 2019;68:1473–84. https://doi.org/10.2337/db18-1243.
64. Mráz M, Cinkajzlová A, Kloučková J, Lacinová Z, Kratochvílová H, Lipš M, et al. Dendritic cells in subcutaneous and epicardial adipose tissue of subjects with type 2 diabetes, obesity, and coronary artery disease. Mediators Inflamm. 2019;2019:5481725. https://doi.org/10.1155/2019/5481725.
65. Hannibal TD, Schmidt-Christensen A, Nilsson J, Fransén-Pettersson N, Hansen L, Holmberg D. Deficiency in plasmacytoid dendritic cells and type I interferon signalling prevents diet-induced obesity and insulin resistance in mice. Diabetologia. 2017;60:2033–41. https://doi.org/10.1007/s00125-017-4341-0.
66. Dalmas E, Venteclef N, Caer C, Poitou C, Cremer I, Aron-Wisnewsky J, et al. T cell-derived IL-22 amplifies IL-1β-driven inflammation in human adipose tissue: relevance to obesity and type 2 diabetes. Diabetes. 2014;63:1966–77. https://doi.org/10.2337/db13-1511.
67. Liu M-H, Li Y, Han L, Zhang Y-Y, Wang D, Wang Z-H, et al. Adipose-derived stem cells were impaired in restricting CD4 + T cell proliferation and polarization in type 2 diabetic ApoE-/- mouse. Mol Immunol. 2017;87:152–60. https://doi.org/10.1016/j.molimm.2017.03.020.
68. Ilan Y, Maron R, Tukpah A-M, Maioli TU, Murugaiyan G, Yang K, et al. Induction of regulatory T cells decreases adipose inflammation and alleviates insulin resistance in Ob/ob mice. Proc Natl Acad Sci U S A. 2010;107:9765–70. https://doi.org/10.1073/pnas.0908771107.
69. Ye L, Liang S, Guo C, Yu X, Zhao J, Zhang H, et al. Inhibition of M1 macrophage activation in adipose tissue by Berberine improves insulin resistance. Life Sci. 2016;166:82–91. https://doi.org/10.1016/j.lfs.2016.09.025.
70. Xiong X-Q, Geng Z, Zhou B, Zhang F, Han Y, Zhou Y-B, et al. FNDC5 attenuates adipose tissue inflammation and insulin resistance via AMPK-mediated macrophage polarization in obesity. Metabolism. 2018;83:31–41. https://doi.org/10.1016/j.metabol.2018.01.013.
71. Ying W, Gao H, Dos Reis FCG, Bandyopadhyay G, Ofrecio JM, Luo Z, et al. MiR-690, an exosomal-derived MiRNA from M2-polarized macrophages, improves insulin sensitivity in obese mice. Cell Metab. 2021;33:781–e7905. https://doi.org/10.1016/j.cmet.2020.12.019.
72. Ruggiero AD, Key C-CC, Kavanagh K. Adipose tissue macrophage polarization in healthy and unhealthy obesity. Front Nutr. 2021;8:625331. https://doi.org/10.3389/fnut.2021.625331.

73. Stafeev I, Podkuychenko N, Michurina S, Sklyanik I, Panevina A, Shestakova E, et al. Low proliferative potential of adipose-derived stromal cells associates with hypertrophy and inflammation in subcutaneous and omental adipose tissue of patients with type 2 diabetes mellitus. J Diabetes Complications. 2019;33:148–59. https://doi.org/10.1016/j.jdiacomp.2018.10.011.
74. Kanda H, Tateya S, Tamori Y, Kotani K, Hiasa K, Kitazawa R, et al. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. J Clin Invest. 2006;116:1494–505. https://doi.org/10.1172/JCI26498.
75. Han MS, White A, Perry RJ, Camporez J-P, Hidalgo J, Shulman GI, et al. Regulation of adipose tissue inflammation by Interleukin 6. Proc Natl Acad Sci U S A. 2020;117:2751–60. https://doi.org/10.1073/pnas.1920004117.
76. Murano I, Barbatelli G, Parisani V, Latini C, Muzzonigro G, Castellucci M, et al. Dead adipocytes, detected as crown-like structures, are prevalent in visceral fat depots of genetically obese mice. J Lipid Res. 2008;49:1562–8. https://doi.org/10.1194/jlr.M800019-JLR200.
77. Lindhorst A, Raulien N, Wieghofer P, Eilers J, Rossi FMV, Bechmann I, et al. Adipocyte death triggers a pro-inflammatory response and induces metabolic activation of resident macrophages. Cell Death Dis. 2021;12:579. https://doi.org/10.1038/s41419-021-03872-9.
78. Altintas MM, Azad A, Nayer B, Contreras G, Zaias J, Faul C, et al. Mast cells, macrophages, and crown-like structures distinguish subcutaneous from visceral fat in mice. J Lipid Res. 2011;52:480–8. https://doi.org/10.1194/jlr.M011338.
79. van Beek L, Lips MA, Visser A, Pijl H, Ioan-Facsinay A, Toes R, et al. Increased systemic and adipose tissue inflammation differentiates obese women with T2DM from obese women with normal glucose tolerance. Metabolism. 2014;63:492–501. https://doi.org/10.1016/j.metabol.2013.12.002.
80. Al-Ghadban S, Bunnell BA. Adipose Tissue-Derived stem cells: Immunomodulatory effects and therapeutic potential. Physiol (Bethesda). 2020;35:125–33. https://doi.org/10.1152/physiol.00021.2019.
81. Serena C, Keiran N, Ceperuelo-Mallafre V, Ejarque M, Fradera R, Roche K, et al. Obesity and type 2 diabetes alters the immune properties of human adipose derived stem cells. Stem Cells. 2016;34:2559–73. https://doi.org/10.1002/stem.2429.
82. DeFuria J, Belkina AC, Jagannathan-Bogdan M, Snyder-Cappione J, Carr JD, Nersesova YR, et al. B cells promote inflammation in obesity and type 2 diabetes through regulation of T-cell function and an inflammatory cytokine profile. Proc Natl Acad Sci U S A. 2013;110:5133–8. https://doi.org/10.1073/pnas.1215840110.
83. Rouault C, Marcelin G, Adriouch S, Rose C, Genser L, Ambrosini M, et al. Senescence-associated β-galactosidase in subcutaneous adipose tissue associates with altered glycaemic status and truncal fat in severe obesity. Diabetologia. 2021;64:240–54. https://doi.org/10.1007/s00125-020-05307-0.
84. Halleux CM, Declerck PJ, Tran SL, Detry R, Brichard SM. Hormonal control of plasminogen activator inhibitor-1 gene expression and production in human adipose tissue: stimulation by glucocorticoids and Inhibition by catecholamines. J Clin Endocrinol Metab. 1999;84:4097–105. https://doi.org/10.1210/jcem.84.11.6127.
85. He G, Bruun JM, Lihn AS, Pedersen SB, Richelsen B. Stimulation of PAI-1 and adipokines by glucose in human adipose tissue in vitro. Biochem Biophys Res Commun. 2003;310:878–83. https://doi.org/10.1016/j.bbrc.2003.09.091.
86. Minamino T, Orimo M, Shimizu I, Kunieda T, Yokoyama M, Ito T, et al. A crucial role for adipose tissue p53 in the regulation of insulin resistance. Nat Med. 2009;15:1082–7. https://doi.org/10.1038/nm.2014.
87. Liu Z, Jin L, Yang J-K, Wang B, Wu KKL, Hallenborg P, et al. The dysfunctional MDM2–p53 axis in adipocytes contributes to Aging-Related metabolic complications by induction of lipodystrophy. Diabetes. 2018;67:2397–409. https://doi.org/10.2337/db18-0684.
88. Spinelli R, Florese P, Parrillo L, Zatterale F, Longo M, D'Esposito V, et al. ZMAT3 hypomethylation contributes to early senescence of preadipocytes from healthy first-degree relatives of type 2 diabetics. Aging Cell. 2022;21:e13557. https://doi.org/10.1111/acel.13557.
89. Agareva M, Stafeev I, Michurina S, Sklyanik I, Shestakova E, Ratner E, et al. Type 2 diabetes mellitus facilitates shift of Adipose-Derived stem cells ex vivo differentiation toward osteogenesis among patients with obesity. Life (Basel). 2022;12:688. https://doi.org/10.3390/life12050688.
90. Ahmad F, Lindh R, Tang Y, Weston M, Degerman E, Manganiello VC. Insulin-induced formation of macromolecular complexes involved in activation of Cyclic nucleotide phosphodiesterase 3B (PDE3B) and its interaction with PKB. Biochem J. 2007;404:257–68. https://doi.org/10.1042/BJ20060960.
91. Snyder PB, Esselstyn JM, Loughney K, Wolda SL, Florio VA. The role of Cyclic nucleotide phosphodiesterases in the regulation of adipocyte lipolysis. J Lipid Res. 2005;46:494–503. https://doi.org/10.1194/jlr.M400362-JLR200.
92. Bódis K, Jelenik T, Lundbom J, Markgraf DF, Strom A, Zaharia O-P, et al. Expansion and impaired mitochondrial efficiency of deep subcutaneous adipose tissue in Recent-Onset type 2 diabetes. J Clin Endocrinol Metab. 2019;105:e1331–43. https://doi.org/10.1210/clinem/dgz267.
93. Adina-Zada A, Zeczycki TN, St Maurice M, Jitrapakdee S, Cleland WW, Attwood PV. Allosteric regulation of the biotin-dependent enzyme pyruvate carboxylase by acetyl-CoA. Biochem Soc Trans. 2012;40:567–72. https://doi.org/10.1042/BST20120041.
94. Massillon D, Barzilai N, Hawkins M, Prus-Wertheimer D, Rossetti L. Induction of hepatic glucose-6-phosphatase gene expression by lipid infusion. Diabetes. 1997;46:153–7. https://doi.org/10.2337/diab.46.1.153.
95. Jocken JWE, Goossens GH, Boon H, Mason RR, Essers Y, Havekes B, et al. Insulin-mediated suppression of lipolysis in adipose tissue and skeletal muscle of obese type 2 diabetic men and men with normal glucose tolerance. Diabetologia. 2013;56:2255–65. https://doi.org/10.1007/s00125-013-2995-9.
96. Elkhidir AE, Eltaher HB, Mohamed AO. Association of lipocalin-2 level, glycemic status and obesity in type 2 diabetes mellitus. BMC Res Notes. 2017;10:285. https://doi.org/10.1186/s13104-017-2604-y.
97. Olczyk P, Koprowski R, Komosinska-Vassev K, Jura-Półtorak A, Winsz-Szczotka K, Kuźnik-Trocha K, et al. Adiponectin, leptin, and leptin receptor in obese patients with type 2 diabetes treated with insulin Detemir. Mol: J Synth Chem Nat Prod Chem. 2017;22:1274. https://doi.org/10.3390/molecules22081274.
98. Abdelgadir M, Karlsson AF, Berglund L, Berne C. Low serum adiponectin concentrations are associated with insulin sensitivity independent of obesity in Sudanese subjects with type 2 diabetes mellitus. Diabetol Metab Syndr. 2013;5:15. https://doi.org/10.1186/1758-5996-5-15.
99. Baig M, Gazzaz ZJ, Bakarman MA, Alzahrani SH. Correlation of serum Vaspin, omentin-1, and adiponectin with metabolic phenotypes in type-2 diabetes mellitus patients. Pak J Med Sci. 2021;37:1762–7. https://doi.org/10.12669/pjms.37.7.4330.
100. Yu S, Zhang Y, Li M, Xu H, Wang Q, Song J, et al. Chemerin and Apelin are positively correlated with inflammation in obese type 2 diabetic patients. Chin Med J. 2012;125:3440. https://doi.org/10.3760/cma.j.issn.0366-6999.2012.19.015.
101. Cavallo MG, Sentinelli F, Barchetta I, Costantino C, Incani M, Perra L, et al. Altered glucose homeostasis is associated with increased serum Apelin levels in type 2 diabetes mellitus. PLoS ONE. 2012;7:e51236. https://doi.org/10.1371/journal.pone.0051236.
102. Srinivasan M, Meadows ML, Maxwell L. Assessment of salivary adipokines resistin, visfatin, and Ghrelin as type 2 diabetes mellitus biomarkers. Biochem Res Int. 2018;2018:7463796. https://doi.org/10.1155/2018/7463796.
103. Mashili FL, Austin RL, Deshmukh AS, Fritz T, Caidahl K, Bergdahl K, et al. Direct effects of FGF21 on glucose uptake in human skeletal muscle: implications for type 2 diabetes and obesity. Diabetes Metab Res Rev. 2011;27:286–97. https://doi.org/10.1002/dmrr.1177.
104. Chen W-W, Li L, Yang G-Y, Li K, Qi X-Y, Zhu W, et al. Circulating FGF-21 levels in normal subjects and in newly diagnose patients with type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2008;116:65–8. https://doi.org/10.1055/s-2007-985148.
105. Huang Y, Yang Z, Ye Z, Li Q, Wen J, Tao X, et al. Lipocalin-2, glucose metabolism and chronic low-grade systemic inflammation in Chinese people. Cardiovasc Diabetol. 2012;11:11. https://doi.org/10.1186/1475-2840-11-11.
106. Munhoz AC, Serna JDC, Vilas-Boas EA, Caldeira da Silva CC, Santos TG, Mosele FC, et al. Adiponectin reverses β-Cell damage and impaired insulin secretion induced by obesity. Aging Cell. 2023;22:e13827. https://doi.org/10.1111/acel.13827.
107. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med. 2002;8:1288–95. https://doi.org/10.1038/nm788.
108. Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, et al. Globular adiponectin protected Ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. J Biol Chem. 2003;278:2461–8. https://doi.org/10.1074/jbc.M209033200.
109. Yoon YS, Ryu D, Lee MW, Hong S, Koo SH. Adiponectin and Thiazolidinedione targets CRTC2 to regulate hepatic gluconeogenesis. Exp Mol Med. 2009;41:577–83. https://doi.org/10.3858/emm.2009.41.8.063.

110. Herzig S, Long F, Jhala US, Hedrick S, Quinn R, Bauer A, et al. CREB regulates hepatic gluconeogenesis through the coactivator PGC-1. Nature. 2001;413:179–83. https://doi.org/10.1038/35093131.
111. Jung D, Bucher F, Ryu S, Jeong J, Lee BY, Jeong Y, et al. An adiponectin receptor agonist antibody stimulates glucose uptake and fatty-acid oxidation by activating AMP-activated protein kinase. Cytokine. 2020;126:154863. https://doi.org/10.1016/j.cyto.2019.154863.
112. Zhao S, Zhu Y, Schultz RD, Li N, He Z, Zhang Z, et al. Partial leptin reduction as an insulin sensitization and weight loss strategy. Cell Metabol. 2019;30:706. https://doi.org/10.1016/j.cmet.2019.08.005.
113. Liu S, Duan R, Wu Y, Du F, Zhang J, Li X, et al. Effects of Vaspin on insulin resistance in rats and underlying mechanisms. Sci Rep. 2018;8:13542. https://doi.org/10.1038/s41598-018-31923-3.
114. Liu S, Li X, Wu Y, Duan R, Zhang J, Du F, et al. Effects of Vaspin on pancreatic B cell secretion via PI3K/Akt and NF-κB signaling pathways. PLoS ONE. 2017;12:e0189722. https://doi.org/10.1371/journal.pone.0189722.
115. Brunetti L, Leone S, Orlando G, Ferrante C, Recinella L, Chiavaroli A, et al. Hypotensive effects of omentin-1 related to increased adiponectin and decreased interleukin-6 in intra-thoracic pericardial adipose tissue. Pharmacol Rep. 2014;66:991–5. https://doi.org/10.1016/j.pharep.2014.06.014.
116. Yang R-Z, Lee M-J, Hu H, Pray J, Wu H-B, Hansen BC, et al. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. Am J Physiol Endocrinol Metab. 2006;290:E1253–1261. https://doi.org/10.1152/ajpendo.00572.2004.
117. Takahashi M, Takahashi Y, Takahashi K, Zolotaryov FN, Hong KS, Kitazawa R, et al. Chemerin enhances insulin signaling and potentiates insulin-stimulated glucose uptake in 3T3-L1 adipocytes. FEBS Lett. 2008;582:573–8. https://doi.org/10.1016/j.febslet.2008.01.023.
118. Sell H, Laurencikiene J, Taube A, Eckardt K, Cramer A, Horrighs A, et al. Chemerin is a novel adipocyte-derived factor inducing insulin resistance in primary human skeletal muscle cells. Diabetes. 2009;58:2731–40. https://doi.org/10.2337/db09-0277.
119. Cui J, Wang M, Zhang W, Sun J, Zhang Y, Zhao L, et al. Enhancing insulin sensitivity in type 2 diabetes mellitus using apelin-loaded small extracellular vesicles from Wharton's jelly-derived mesenchymal stem cells: a novel therapeutic approach. Diabetol Metab Syndr. 2024;16:84. https://doi.org/10.1186/s13098-024-01332-w.
120. Gourdy P, Cazals L, Thalamas C, Sommet A, Calvas F, Galitzky M, et al. Apelin administration improves insulin sensitivity in overweight men during hyperinsulinaemic-euglycaemic clamp. Diabetes Obes Metab. 2018;20:157–64. https://doi.org/10.1111/dom.13055.
121. Feng J, Zhao H, Du M, Wu X. The effect of apelin-13 on pancreatic islet beta cell mass and myocardial fatty acid and glucose metabolism of experimental type 2 diabetic rats. Peptides. 2019;114:1–7. https://doi.org/10.1016/j.peptides.2019.03.006.
122. Steppan CM, Wang J, Whiteman EL, Birnbaum MJ, Lazar MA. Activation of SOCS-3 by resistin. Mol Cell Biol. 2005;25:1569–75. https://doi.org/10.1128/MCB.25.4.1569-1575.2005.
123. Jørgensen SB, Honeyman J, Oakhill JS, Fazakerley D, Stöckli J, Kemp BE, et al. Oligomeric resistin impairs insulin and AICAR-stimulated glucose uptake in mouse skeletal muscle by inhibiting GLUT4 translocation. Am J Physiol Endocrinol Metab. 2009;297:E57–66. https://doi.org/10.1152/ajpendo.90744.2008.
124. Palanivel R, Maida A, Liu Y, Sweeney G. Regulation of insulin signalling, glucose uptake and metabolism in rat skeletal muscle cells upon prolonged exposure to resistin. Diabetologia. 2006;49:183–90. https://doi.org/10.1007/s00125-005-0060-z.
125. Li F-P, He J, Li Z-Z, Luo Z-F, Yan L, Li Y. Effects of resistin expression on glucose metabolism and hepatic insulin resistance. Endocrine. 2009;35:243–51. https://doi.org/10.1007/s12020-009-9148-4.
126. Song R, Wang X, Mao Y, Li H, Li Z, Xu W, et al. Resistin disrupts glycogen synthesis under high insulin and high glucose levels by down-regulating the hepatic levels of GSK3β. Gene. 2013;529:50–6. https://doi.org/10.1016/j.gene.2013.06.085.
127. Heo YJ, Choi S-E, Jeon JY, Han SJ, Kim DJ, Kang Y, et al. Visfatin induces inflammation and insulin resistance via the NF-κB and STAT3 signaling pathways in hepatocytes. J Diabetes Res. 2019;2019:4021623. https://doi.org/10.1155/2019/4021623.
128. Sun Q, Li L, Li R, Yang M, Liu H, Nowicki MJ, et al. Overexpression of Visfatin/PBEF/Nampt alters whole-body insulin sensitivity and lipid profile in rats. Ann Med. 2009;41:311–20. https://doi.org/10.1080/07853890902729760.
129. Kim DS, Kang S, Moon NR, Park S. Central visfatin potentiates glucose-stimulated insulin secretion and β-cell mass without increasing serum visfatin levels in diabetic rats. Cytokine. 2014;65:159–66. https://doi.org/10.1016/j.cyto.2013.11.008.
130. Kaufman A, Abuqayyas L, Denney WS, Tillman EJ, Rolph T. AKR-001, an Fc-FGF21 analog, showed sustained pharmacodynamic effects on insulin sensitivity and lipid metabolism in type 2 diabetes patients. Cell Rep Med. 2020;1:100057. https://doi.org/10.1016/j.xcrm.2020.100057.
131. Ye X, Qi J, Yu D, Wu Y, Zhu S, Li S, et al. Pharmacological efficacy of FGF21 analogue, liraglutide and insulin glargine in treatment of type 2 diabetes. J Diabetes Complicat. 2017;31:726–34. https://doi.org/10.1016/j.jdiacomp.2017.01.008.
132. Kamble PG, Pereira MJ, Sidibeh CO, Amini S, Sundbom M, Börjesson JL, et al. Lipocalin 2 produces insulin resistance and can be upregulated by glucocorticoids in human adipose tissue. Mol Cell Endocrinol. 2016;427:124–32. https://doi.org/10.1016/j.mce.2016.03.011.
133. Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med. 2007;13:332–9. https://doi.org/10.1038/nm1557.
134. Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, et al. Effects of the obese gene product on body weight regulation in Ob/ob mice. Science. 1995;269:540–3. https://doi.org/10.1126/science.7624776.
135. Kitamura T, Feng Y, Kitamura YI, Chua SC, Xu AW, Barsh GS, et al. Forkhead protein FoxO1 mediates Agrp-dependent effects of leptin on food intake. Nat Med. 2006;12:534–40. https://doi.org/10.1038/nm1392.
136. Marcelin G, Jo Y-H, Li X, Schwartz GJ, Zhang Y, Dun NJ, et al. Central action of FGF19 reduces hypothalamic AGRP/NPY neuron activity and improves glucose metabolism. Mol Metab. 2014;3:19–28. https://doi.org/10.1016/j.molmet.2013.10.002.
137. Nazarians-Armavil A, Menchella JA, Belsham DD. Cellular insulin resistance disrupts Leptin-Mediated control of neuronal signaling and transcription. Mol Endocrinol. 2013;27:990–1003. https://doi.org/10.1210/me.2012-1338.
138. Xie Q, Deng Y, Huang C, Liu P, Yang Y, Shen W, et al. Chemerin-induced mitochondrial dysfunction in skeletal muscle. J Cell Mol Med. 2015;19:986–95. https://doi.org/10.1111/jcmm.12487.
139. Fang P, Han L, Yu M, Han S, Wang M, Huang Y, et al. Development of metabolic dysfunction in mice lacking chemerin. Mol Cell Endocrinol. 2021;535:111369. https://doi.org/10.1016/j.mce.2021.111369.
140. Tatemoto K, Hosoya M, Habata Y, Fujii R, Kakegawa T, Zou MX, et al. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. Biochem Biophys Res Commun. 1998;251:471–6. https://doi.org/10.1006/bbrc.1998.9489.
141. Noori-Zadeh A, Bakhtiyari S, Khanjari S, Haghani K, Darabi S. Elevated blood Apelin levels in type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes Res Clin Pract. 2019;148:43–53. https://doi.org/10.1016/j.diabres.2018.12.012.
142. Fasshauer M, Blüher M. Adipokines in health and disease. Trends Pharmacol Sci. 2015;36:461–70. https://doi.org/10.1016/j.tips.2015.04.014.
143. Mir MM, Mir R, Alghamdi MAA, Wani JI, Sabah ZU, Jeelani M, et al. Differential association of selected adipocytokines, adiponectin, leptin, resistin, visfatin and Chemerin, with the pathogenesis and progression of type 2 diabetes mellitus (T2DM) in the Asir region of Saudi Arabia: A case control study. J Pers Med. 2022;12:735. https://doi.org/10.3390/jpm12050735.
144. Radzicka-Mularczyk S, Zaborowski MP, Brązert J, Pietryga M. Serum visfatin as a metabolic biomarker in obese patients with gestational diabetes mellitus. Minerva Endocrinol (Torino). 2021;46:396–405. https://doi.org/10.23736/S2724-6507.20.03280-0.
145. Oki K, Yamane K, Kamei N, Nojima H, Kohno N. Circulating visfatin level is correlated with inflammation, but not with insulin resistance. Clin Endocrinol (Oxf). 2007;67:796–800. https://doi.org/10.1111/j.1365-2265.2007.02966.x.
146. Jiang Y-K, Deng H-Y, Qiao Z-Y, Gong F-X. Visfatin level and gestational diabetes mellitus: a systematic review and meta-analysis. Arch Physiol Biochem. 2021;127:468–78. https://doi.org/10.1080/13813455.2021.1874997.
147. Mraz M, Bartlova M, Lacinova Z, Michalsky D, Kasalicky M, Haluzikova D, et al. Serum concentrations and tissue expression of a novel endocrine regulator fibroblast growth factor-21 in patients with type 2 diabetes and obesity. Clin Endocrinol (Oxf). 2009;71:369–75. https://doi.org/10.1111/j.1365-2265.2008.03502.x.
148. Charles ED, Neuschwander-Tetri BA, Frias JP, Kundu S, Luo Y, Tirucherai GS, et al. Pegbelfermin (BMS-986036), pegylated FGF21, in patients with obesity and

type 2 diabetes: results from a randomized phase 2 study. Obes (Silver Spring Md). 2018;27:41. https://doi.org/10.1002/oby.22344.
149. Badman MK, Koester A, Flier JS, Kharitonenkov A, Maratos-Flier E. Fibroblast growth factor 21-deficient mice demonstrate impaired adaptation to ketosis. Endocrinology. 2009;150:4931–40. https://doi.org/10.1210/en.2009-0532.
150. Law IK, Xu A, Lam KS, Berger T, Mak TW, Vanhoutte PM, et al. Lipocalin-2 deficiency attenuates insulin resistance associated with aging and obesity. Diabetes. 2010;59:872. https://doi.org/10.2337/db09-1541.
151. Skovsø S, Damgaard J, Fels JJ, Olsen GS, Wolf XA, Rolin B, et al. Effects of insulin therapy on weight gain and fat distribution in the HF/HS-STZ rat model of type 2 diabetes. Int J Obes. 2015;39:1531–8. https://doi.org/10.1038/ijo.2015.92.
152. Shah PK, Mudaliar S, Chang AR, Aroda V, Andre M, Burke P, et al. Effects of intensive insulin therapy alone and in combination with Pioglitazone on body weight, composition, distribution and liver fat content in patients with type 2 diabetes. Diabetes Obes Metab. 2011;13:505–10. https://doi.org/10.1111/j.1463-1326.2011.01370.x.
153. Circulating C1q/TNF-Related Protein 3. Omentin-1 and NGAL in Obese Patients with Type 2 Diabetes During Insulin Therapy - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/31195747/ (accessed January 5, 2024).
154. Pedersen O, Hother-Nielsen O, Bak J, Hjollund E, Beck-Nielsen H. Effects of sulfonylureas on adipocyte and skeletal muscle insulin action in patients with non-insulin-dependent diabetes mellitus. Am J Med. 1991;90:S22–8. https://doi.org/10.1016/0002-9343(91)90414-s.
155. Abbasi F, Kamath V, Rizvi AA, Carantoni M, Chen YD, Reaven GM. Results of a placebo-controlled study of the metabolic effects of the addition of Metformin to sulfonylurea-treated patients. Evidence for a central role of adipose tissue. Diabetes Care. 1997;20:1863–9. https://doi.org/10.2337/diacare.20.12.1863.
156. Mori Y, Komiya H, Kurokawa N, Tajima N. Comparison of the effects of glimepiride and Glibenclamide on adipose tissue tumour necrosis factor-alpha mRNA expression and cellularity. Diabetes Obes Metab. 2004;6:28–34. https://doi.org/10.1111/j.1463-1326.2004.00305.x.
157. Eriksson A, Attvall S, Bonnier M, Eriksson JW, Rosander B, Karlsson FA. Short-term effects of Metformin in type 2 diabetes. Diabetes Obes Metab. 2007;9:483–9. https://doi.org/10.1111/j.1463-1326.2006.00624.x.
158. Virtanen KA, Hällsten K, Parkkola R, Janatuinen T, Lönnqvist F, Viljanen T, et al. Differential effects of Rosiglitazone and Metformin on adipose tissue distribution and glucose uptake in type 2 diabetic subjects. Diabetes. 2003;52:283–90. https://doi.org/10.2337/diabetes.52.2.283.
159. Zsóri G, Illés D, Iványi E, Kosár K, Holzinger G, Tajti M, et al. In New-Onset diabetes mellitus, Metformin reduces fat accumulation in the liver, but not in the pancreas or pericardium. Metab Syndr Relat Disord. 2019;17:289–95. https://doi.org/10.1089/met.2018.0086.
160. Abad-Jiménez Z, López-Domènech S, Díaz-Rúa R, Iannantuoni F, Gómez-Abril SÁ, Periañez-Gómez D, et al. Systemic oxidative stress and visceral adipose tissue mediators of NLRP3 inflammasome and autophagy are reduced in obese type 2 diabetic patients treated with Metformin. Antioxid (Basel). 2020;9:892. https://doi.org/10.3390/antiox9090892.
161. Lund SS, Tarnow L, Frandsen M, Smidt UM, Pedersen O, Parving H-H, et al. Impact of Metformin versus the prandial insulin secretagogue, repaglinide, on fasting and postprandial glucose and lipid responses in non-obese patients with type 2 diabetes. Eur J Endocrinol. 2008;158:35–46. https://doi.org/10.1530/EJE-07-0500.
162. Dutour A, Abdesselam I, Ancel P, Kober F, Mrad G, Darmon P, et al. Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy. Diabetes Obes Metab. 2016;18:882–91. https://doi.org/10.1111/dom.12680.
163. Yan P, Li L, Yang M, Liu D, Liu H, Boden G, et al. Effects of the long-acting human glucagon-like peptide-1 analog liraglutide on plasma omentin-1 levels in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2011;92:368–74. https://doi.org/10.1016/j.diabres.2011.02.030.
164. van Eyk HJ, Paiman EHM, Bizino MB, de Heer P, Geelhoed-Duijvestijn PH, Kharagjitsingh AV, et al. A double-blind, placebo-controlled, randomised trial to assess the effect of liraglutide on ectopic fat accumulation in South Asian type 2 diabetes patients. Cardiovasc Diabetol. 2019;18:87. https://doi.org/10.1186/s12933-019-0890-5.
165. Volpe S, Lisco G, Fanelli M, Racaniello D, Colaianni V, Lavarra V, et al. Oral semaglutide improves body composition and preserves lean mass in patients with type 2 diabetes: a 26-week prospective real-life study. Front Endocrinol (Lausanne). 2023;14:1240263. https://doi.org/10.3389/fendo.2023.1240263.
166. Volpe S, Lisco G, Fanelli M, Racaniello D, Colaianni V, Triggiani D, et al. Once-Weekly subcutaneous semaglutide improves fatty liver disease in patients with type 2 diabetes: A 52-Week prospective Real-Life study. Nutrients. 2022;14:4673. https://doi.org/10.3390/nu14214673.
167. Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á. Effect of Tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. Lancet Diabetes Endocrinol. 2022;10:393–406. https://doi.org/10.1016/S2213-8587(22)00070-5.
168. Kolak M, Yki-Järvinen H, Kannisto K, Tiikkainen M, Hamsten A, Eriksson P, et al. Effects of chronic Rosiglitazone therapy on gene expression in human adipose tissue in vivo in patients with type 2 diabetes. J Clin Endocrinol Metab. 2007;92:720–4. https://doi.org/10.1210/jc.2006-1465.
169. Hwang Y-C, Lee EY, Lee WJ, Cha BS, Yoon K-H, Park KS, et al. Effects of Rosiglitazone on body fat distribution and insulin sensitivity in Korean type 2 diabetes mellitus patients. Metabolism. 2008;57:479–87. https://doi.org/10.1016/j.metabol.2007.11.008.
170. Tiikkainen M, Häkkinen A-M, Korsheninnikova E, Nyman T, Mäkimattila S, Yki-Järvinen H. Effects of Rosiglitazone and Metformin on liver fat content, hepatic insulin resistance, insulin clearance, and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes. 2004;53:2169–76. https://doi.org/10.2337/diabetes.53.8.2169.
171. Doležalová R, Haluzík MM, Bošanská L, Lacinová Z, Kasalová Z, Stulc T, et al. Effect of PPAR-gamma agonist treatment on markers of endothelial dysfunction in patients with type 2 diabetes mellitus. Physiol Res. 2007;56:741–8. https://doi.org/10.33549/physiolres.931060.
172. McGee KC, Harte AL, da Silva NF, Al-Daghri N, Creely SJ, Kusminski CM, et al. Visfatin is regulated by Rosiglitazone in type 2 diabetes mellitus and influenced by NFκB and JNK in human abdominal subcutaneous adipocytes. PLoS ONE. 2011;6:e20287. https://doi.org/10.1371/journal.pone.0020287.
173. Jung HS, Youn B-S, Cho YM, Yu K-Y, Park HJ, Shin CS, et al. The effects of Rosiglitazone and Metformin on the plasma concentrations of resistin in patients with type 2 diabetes mellitus. Metabolism. 2005;54:314–20. https://doi.org/10.1016/j.metabol.2004.05.019.
174. Tan GD, Fielding BA, Currie JM, Humphreys SM, Désage M, Frayn KN, et al. The effects of Rosiglitazone on fatty acid and triglyceride metabolism in type 2 diabetes. Diabetologia. 2005;48:83–95. https://doi.org/10.1007/s00125-004-1619-9.
175. Kelly IE, Han TS, Walsh K, Lean ME. Effects of a Thiazolidinedione compound on body fat and fat distribution of patients with type 2 diabetes. Diabetes Care. 1999;22:288–93. https://doi.org/10.2337/diacare.22.2.288.
176. Kawai T, Takei I, Oguma Y, Ohashi N, Tokui M, Oguchi S, et al. Effects of troglitazone on fat distribution in the treatment of male type 2 diabetes. Metabolism. 1999;48:1102–7. https://doi.org/10.1016/s0026-0495(99)90122-1.
177. Mori Y, Murakawa Y, Okada K, Horikoshi H, Yokoyama J, Tajima N, et al. Effect of troglitazone on body fat distribution in type 2 diabetic patients. Diabetes Care. 1999;22:908–12. https://doi.org/10.2337/diacare.22.6.908.
178. Akazawa S, Sun F, Ito M, Kawasaki E, Eguchi K. Efficacy of troglitazone on body fat distribution in type 2 diabetes. Diabetes Care. 2000;23:1067–71. https://doi.org/10.2337/diacare.23.8.1067.
179. Tripathy D, Daniele G, Fiorentino TV, Perez-Cadena Z, Chavez-Velasquez A, Kamath S, et al. Pioglitazone improves glucose metabolism and modulates skeletal muscle TIMP-3-TACE dyad in type 2 diabetes mellitus: a randomised, double-blind, placebo-controlled, mechanistic study. Diabetologia. 2013;56:2153–63. https://doi.org/10.1007/s00125-013-2976-z.
180. Hirose H, Kawai T, Yamamoto Y, Taniyama M, Tomita M, Matsubara K, et al. Effects of Pioglitazone on metabolic parameters, body fat distribution, and serum adiponectin levels in Japanese male patients with type 2 diabetes. Metabolism. 2002;51:314–7. https://doi.org/10.1053/meta.2002.30506.
181. Hartemann-Heurtier A, Halbron M, Golmard J-L, Jacqueminet S, Bastard J-P, Rouault C, et al. Effects of bed-time insulin versus Pioglitazone on abdominal fat accumulation, inflammation and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes Res Clin Pract. 2009;86:37–43. https://doi.org/10.1016/j.diabres.2009.06.028.
182. Hao Z, Sun Y, Li G, Shen Y, Wen Y, Liu Y. Effects of Canagliflozin and Metformin on insulin resistance and visceral adipose tissue in people with newly-diagnosed type 2 diabetes. BMC Endocr Disord. 2022;22:37. https://doi.org/10.1186/s12902-022-00949-0.

183. Park HK, Kim K-A, Min K-W, Sohn T-S, Jeong IK, Ahn CW, et al. Effects of Dapagliflozin compared with glimepiride on body composition in Asian patients with type 2 diabetes inadequately controlled with metformin: the BEYOND study. Diabetes Obes Metab. 2023;25:2743–55. https://doi.org/10.1111/dom.15164.
184. Rajeev SP, Roberts CA, Brown E, Sprung VS, Harrold JA, Halford JCG, et al. No evidence of compensatory changes in energy balance, despite reductions in body weight and liver fat, during Dapagliflozin treatment in type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled, cross-over trial (ENERGIZE). Diabetes Obes Metab. 2023;25:3621–31. https://doi.org/10.1111/dom.15257.
185. Johansson L, Hockings PD, Johnsson E, Dronamraju N, Maaske J, Garcia-Sanchez R, et al. Dapagliflozin plus saxagliptin add-on to Metformin reduces liver fat and adipose tissue volume in patients with type 2 diabetes. Diabetes Obes Metab. 2020;22:1094–101. https://doi.org/10.1111/dom.14004.
186. Aragón-Herrera A, Moraña-Fernández S, Otero-Santiago M, Anido-Varela L, Campos-Toimil M, García-Seara J, et al. The lipidomic and inflammatory profiles of visceral and subcutaneous adipose tissues are distinctly regulated by the SGLT2 inhibitor empagliflozin in Zucker diabetic fatty rats. Biomed Pharmacother. 2023;161:114535. https://doi.org/10.1016/j.biopha.2023.114535.
187. Gaborit B, Ancel P, Abdullah AE, Maurice F, Abdesselam I, Calen A, et al. Effect of empagliflozin on ectopic fat stores and myocardial energetics in type 2 diabetes: the EMPACEF study. Cardiovasc Diabetol. 2021;20:57. https://doi.org/10.1186/s12933-021-01237-2.
188. Kinoshita T, Shimoda M, Nakashima K, Fushimi Y, Hirata Y, Tanabe A, et al. Comparison of the effects of three kinds of glucose-lowering drugs on non-alcoholic fatty liver disease in patients with type 2 diabetes: A randomized, open-label, three-arm, active control study. J Diabetes Investig. 2020;11:1612–22. https://doi.org/10.1111/jdi.13279.
189. Zhang T, He J, Xu C, Zu L, Jiang H, Pu S, et al. Mechanisms of Metformin inhibiting lipolytic response to isoproterenol in primary rat adipocytes. J Mol Endocrinol. 2009;42:57–66. https://doi.org/10.1677/JME-08-0130.
190. Metais C, Forcheron F, Abdallah P, Basset A, Del Carmine P, Bricca G, et al. Adiponectin receptors: expression in Zucker diabetic rats and effects of Fenofibrate and Metformin. Metabolism. 2008;57:946–53. https://doi.org/10.1016/j.metabol.2008.02.010.
191. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes– state-of-the-art. Mol Metab. 2020;46:101102. https://doi.org/10.1016/j.molmet.2020.101102.
192. Duan K, Yan X, Gao Z, Hou Y, Lv X, Song G. Effect of glucagon-like peptide-1 receptor agonists on fat distribution in patients with type 2 diabetes: A systematic review and meta-analysis. J Diabetes Investig. 2022;13:1149–60. https://doi.org/10.1111/jdi.13775.
193. Kruszynska YT, Mukherjee R, Jow L, Dana S, Paterniti JR, Olefsky JM. Skeletal muscle peroxisome proliferator- activated receptor-gamma expression in obesity and non- insulin-dependent diabetes mellitus. J Clin Invest. 1998;101:543–8. https://doi.org/10.1172/JCI1076.
194. Cadoudal T, Blouin JM, Collinet M, Fouque F, Tan GD, Loizon E, et al. Acute and selective regulation of glyceroneogenesis and cytosolic phosphoenolpyruvate Carboxykinase in adipose tissue by Thiazolidinediones in type 2 diabetes. Diabetologia. 2007;50:666–75. https://doi.org/10.1007/s00125-006-0560-5.
195. Rajeev SP, Cuthbertson DJ, Wilding JPH. Energy balance and metabolic changes with sodium-glucose co-transporter 2 Inhibition. Diabetes Obes Metab. 2016;18:125–34. https://doi.org/10.1111/dom.12578.

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