Central obesity, type 2 diabetes and insulin: exploring a pathway full of thorns

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Abstract

The prevalence of type 2 diabetes (T2D) is rapidly increasing. This is strongly related to the contemporary lifestyle changes that have resulted in increased rates of overweight individuals and obesity. Central (intra-abdominal) obesity is observed in the majority of patients with T2D. It is associated with insulin resistance, mainly at the level of skeletal muscle, adipose tissue and liver. The discovery of macrophage infiltration in the abdominal adipose tissue and the unbalanced production of adipocyte cytokines (adipokines) was an essential step towards novel research perspectives for a better understanding of the molecular mechanisms governing the development of insulin resistance. Furthermore, in an obese state, the increased cellular uptake of non-esterified fatty acids is exacerbated without any subsequent β-oxidation. This in turn contributes to the accumulation of intermediate lipid metabolites that cause defects in the insulin signaling pathway. This paper examines the possible cellular mechanisms that connect central obesity with defects in the insulin pathway. It discusses the discrepancies observed from studies organized in cell cultures, animal models and humans. Finally, it emphasizes the need for therapeutic strategies in order to achieve weight reduction in overweight and obese patients with T2D.

Key words: adipokines, central obesity, cardiovascular disease, insulin resistance, non-esterified fatty acids, type 2 diabetes.

Introduction

The prevalence of type 2 diabetes (T2D) is evolving globally at an alarming rate [1]. It is estimated that by the year 2030 approximately 366 million people will have diabetes and more than 90% of them T2D [2]. The increased prevalence of T2D is strongly related to the contemporary global lifestyle “modernization” (overnutrition, changes in the food environment and a sedentary lifestyle) that has resulted in increased rates of overweight individuals and obesity [3]. The prevalence of T2D is three to seven times higher in obese adults compared to normal-weight ones. Specifically, adults with body mass index (BMI) > 35 kg/m² are 20 times as likely to develop T2D compared to those with a BMI between 18.5 kg/m² and 24.9 kg/m² [4]. It is also estimated that for every 1 kg increase in body weight there is a 4.5% higher risk of developing T2D [5]. Fur-
thermore, obesity-related T2D is increasingly diagnosed in the third decade of life, while in some countries and ethnic populations children and adolescents develop T2D [6].

Both obesity and physical inactivity underlie the development of insulin resistance. Insulin resistance is observed in approximately 90% of patients with T2D and in 66% of individuals with impaired glucose tolerance (IGT). Insulin resistance together with β-cell dysfunction and apoptosis are the two fundamental mechanisms for the development of T2D [7, 8]. Insulin resistance per se doubles the risk for cardiovascular disease, which is the ultimate cause of death in about 80% of patients with T2D. This fact suggests that an important part of the higher cardiovascular risk observed is due to its proatherogenic effects [9, 10]. It has also been correlated with a higher rate of cerebrovascular disease, coronary artery disease (CAD) and peripheral arterial disease (PAD) [11–13].

Central (intra-abdominal) obesity is observed in the majority of patients with T2D. It is associated with insulin resistance, mainly at the level of adipose tissue, liver and skeletal muscle [4, 7]. The discovery of macrophage infiltration in the abdominal adipose tissue and the unbalanced production of adipocyte protein factors and hormones (adipokines) was a major step towards novel research perspectives, allowing for a better understanding of the mechanisms governing the development of insulin resistance. Furthermore, the increased cellular uptake of non-esterified fatty acids (NEFAs) is exacerbated in an obese state without any subsequent β-oxidation. This in turn contributes to the accumulation of intermediate lipid metabolites and causes defects in the insulin signaling pathway [4, 7].

This paper examines the possible cellular mechanisms that connect central obesity with defects in the insulin pathway. It discusses the discrepancies observed from studies organized in cell cultures, animal models and humans. It also emphasizes the need for therapeutic approaches in order to achieve weight reduction in overweight and obese patients with T2D.

Search of literature

We performed the literature search through PubMed, Scope and Google (January 1980–May 2013) and identified the relevant studies to be included in the review. The search terms we used were central obesity, adipokines, insulin resistance, non-esterified fatty acids and T2D.

The insulin pathway in a sensitive and resistant state

Insulin receptor (IR) is a transmembrane protein that is composed of four subunits: two α and two β. In nonvascular cells insulin exerts its activity after binding to the α-subunit at the extracellular surface of the sarcolemmal membrane (Figure 1) [14]. This in turn causes autophosphorylation of the intracellular domain of the IR β-subunit that has tyrosine kinase (TK) activity and a subsequent tyrosine phosphorylation of intracellular adapter proteins, such as IR substrates 1 and 2 (IRS-1 and IRS-2) and Shc [15, 16]. In hepatic cells IRS-2 phosphorylation mediates insulin activity after binding to IR, while in muscle cells IRS-1 serves as the main docking protein for the insulin pathway [15]. Tyrosine-phosphorylated IRS-1 and IRS-2 bind to the src-homology 2 (SH2) domain of intracellular proteins. One of these proteins is the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI 3-kinase). The interaction between the p85 subunit and the phosphorylated IRS promotes activation of the p110 catalytic subunit of PI 3-kinase. The final result of this cascade is activation of the PI 3-kinase pathway by insulin. This pathway is linked to three fundamental metabolic functions of insulin: (i) Glucose transport, through stimulation of sarcolemmal glucose transporter 4 (GLUT-4) to the cell surface. Glucose transport is the rate controlling step for insulin-stimulated muscle glycogen production in patients with T2D. Insulin mediated translocation of GLUT-4 is reduced by 50% in skeletal muscle cells of patients with T2D. This reduction is correlated with the severity of T2D. (ii) Glucose phosphorylation through hexokinase-II stimulation. (iii) Glycogen synthesis via glycogen synthase expression. Hexokinase-II and glycogen synthase activity are reduced when the PI 3-kinase pathway is inhibited [16, 17]. The association of p85 protein with IRS-1 is also highly suppressed in patients with T2D and obese individuals without diabetes compared to lean healthy ones [18].

Activation of the PI 3-kinase pathway has also been linked to the production of nitric oxide (NO), partially due to an increased rate of endothelial nitric oxide synthase (eNOS) gene expression [19]. In vascular cells PI 3-kinase downregulation may suppress the vasodilator effect of insulin via NO production; this in turn causes endothelial dysfunction and promotes the development of hypertension. Furthermore, it stimulates several pro-atherogenic mechanisms. These are mainly vascular smooth muscle cell (VSMC) proliferation and migration, leukocyte adhesion to endothelial cells and platelet aggregation.

Tyrosine-phosphorylated Shc and IRS proteins can also bind to the SH2 domain of GRB2, leading to activation of the extracellular regulated kinase (ERK)/mitogen-activated protein (MAP) kinase signaling pathway [20]. In patients with severe insulin resistance, the cellular events that lead to
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Activation of the PI-3 kinase pathway are inhibited. Increased insulin secretion stimulates the MAP kinase pathway since it is normally sensitive to insulin. Hence, it is excessively hyperactive. MAP kinase pathway activation promotes the growth effects of insulin. It is connected to VSMC proliferation, increased collagen formation, expression of extracellular matrix proteins and the activation of multiple inflammatory pathways. The major pathways involved are the inhibitor \( \kappa B \) (\( \kappa B \)/nuclear factor-\( \kappa B \) (NF-\( \kappa B \)) and c-Jun N-terminal kinase (JNK) [20]. Increased insulin activity through the MAP kinase pathway plays an accelerating role in the development of diabetes-related complications, such as inflammation, proliferation and atherosclerosis. The VSMCs and endothelial cells also express IRs. The IR phosphorylation causes tyrosine phosphorylation of IRS-1, IRS-2 and Shc. In this way both PI 3-kinase and ERK/MAP kinase pathways are activated in a sensitive insulin state.

3-phosphoinositide-dependent protein kinase-1 (PDK-1) is a serine/threonine kinase, ubiquitously expressed in human tissues; it plays a pivotal role in mediating signal transduction downstream of the PI 3-kinase pathway in response to mitogen stimulation [21]. This effect is achieved after the phosphorylation of several kinases that are downstream effectors of PI 3-kinase. The best characterized substrate of PDK-1 is protein kinase B (PKB). At the cellular level, PDK-1 regulates key insulin effects such as GLUT-4 membrane translocation, glycogen synthesis, protein synthesis, and cell survival [22]. Mammalian target of rapamycin (mToR) is a member of the PI kinase-related kinase pathway. It has an essential role in insulin-induced subcellular redistribution of IRS-1. It can also control negatively insulin-stimulated glucose transport, mainly through the redistribution of IRS-1, while the subsequent degradation of IRS-1 downregulates insulin-stimulated activation of Akt [23].

Several genetic mechanisms have been associated with the development of insulin resistance: (i) Polymorphisms of insulin, IRs, IRS-1 and other post-receptor molecules. (ii) Primary target cell defects. (iii) Auto-antibodies against insulin and/or IR. (iv) Accelerated insulin degradation. (v) Mitochondrial dysfunction [23–25]. Acquired effects

**Figure 1.** The insulin pathway in a sensitive and an insulin resistant state. Insulin exerts its activity after binding to the \( \alpha \)-subunit of the insulin receptor (IR) at the extracellular surface of the sarcolemmal membrane. This, in turn, causes the autophosphorylation of the IR \( \beta \)-subunit, which has tyrosine kinase (TK) activity, and subsequent tyrosine phosphorylation of intracellular adapter proteins, such as IR substrates 1 and 2 (IRS-1 and IRS-2). Tyrosine-phosphorylated IRS-1 or IRS-2 bind to the src-homology 2 (SH2) domain of intracellular proteins. One of these proteins is the P85 regulatory subunit of phosphatidylinositol 3-kinase (PI 3-kinase). The interaction between the P85 subunit and the phosphorylated IRS promotes activation of the p110 catalytic subunit of PI 3-kinase. The final result of this cascade is activation of the PI 3-kinase pathway by insulin, which promotes glucose transport through the stimulation of glucose transporter 4 (GLUT-4) to the cell surface. Activation of the PI 3-kinase pathway has also been linked to nitric oxide (NO) production partially due to an increase in the endothelial nitric oxide synthase (eNOS) gene expression. PI 3-kinase downregulation may lessen the vasodilator effect of insulin via NO production and promote endothelial dysfunction. Tyrosine-phosphorylated Shc and IRS proteins can also lead to activation of the mitogen-activated protein (MAP) kinase signaling pathway. Increased insulin activity through the MAP kinase pathway plays an accelerating role in the development of diabetes-related complications, such as inflammation, proliferation and atherosclerosis.
that block insulin activity are mainly age, obesity, lipotoxicity and glucotoxicity [26]. Accumulating evidence suggests an essential role of central obesity in the development of insulin resistance and progressively T2D (Tables I, II).

Adipokines and other molecules that may induce insulin resistance

White adipose tissue (WAT) is mainly white/yellow in color and it is concentrated in the subcutaneous regions and the abdomen [27]. Brown adipose tissue (BAT) is relatively sparse and has its main location in small “pockets” in the thorax [28]. The WAT has a major role in the regulation of fatty acid homeostasis. When calorie abundance is the case, it stores NEFAs in the form of triglycerides (TG). In times of energy lack it releases them back into the circulation [27, 29, 30]. Subcutaneous WAT is by far the largest adipose depot within the human body. Visceral WAT (mainly composed by omental, mesenteric, retroperitoneal and epicardial fat) constitutes about 15% of total fat in obese individuals [27, 31].

The preferable accumulation of macrophages in visceral compared to subcutaneous fat is associated with the secretion of a plethora of bioactive signaling proteins, the adipokines. Adipokines and other molecules predominantly secreted from visceral fat can play an essential role in the development, exacerbation and maintenance of an insulin resistant state. Adipokines have an important contribution to the regulation of local metabolic processes. They mainly have an autocrine and paracrine function. Some of them also regulate systemic processes displaying typical endocrine properties; in this way they establish adipose tissue as an evolving endocrine organ, critical in the regulation of cellular insulin activity [27]. Most of these molecules are associated with the downregulation of IR and mainly with a postreceptor failure to activate its TK activity. The latter is achieved through serine/threonine phosphorylation of IRS-1 and/or IRS-2 and has major impact on the development of insulin resistance (Figure 2) [32].

Tumor necrosis factor-α

The TNF-α is suggested to play a significant role in the development of insulin resistance at the level of adipocyte, hepatocyte and skeletal muscle cell. It is mainly produced from macrophages infiltrating adipose tissue and less so from adipocytes [33]. It decreases the expression of IR and suppresses its autophosphorylation [34]. It also decreases the expression of IRS-1 and GLUT-4, while it promotes a JNK pathway mediated serine phosphorylation of IRS-1 [35]. The TNF-α has a stimulatory effect on lipolysis after downregulation of the lipid droplet-associated protein perilipin, which suppresses the activity of hormone-sensitive lipase [36]. It also causes reduced oxidation of NEFAs in skeletal muscle and hepatocyte cells through suppression of 5’AMP-activated protein kinase (AMPK) and the induction of protein phosphatase 2C [37]. The reduced rate of NEFA oxidation results in increased accumulation of intermediate bioactive lipid metabolites, which in turn inhibit IRS activity [38]. Deletion of TNF-α or TNF-α receptors resulted in an enhanced insulin sensitivity status both in leptin-deficient ob/ob mice and in diet-induced obese mice [34]. Treatment with the TNF-α inhibitor marimastat was also found to improve insulin sensitivity and reverse hepatic steatosis in mouse models of diet-induced obesity and leptin deficiency [39].

TNF-α levels in humans were associated with insulin resistance after adjustment for adiposity and metabolic syndrome status; weight loss was found to decrease TNF-α levels [40]. The extended use of anti-TNF-α therapies in inflammatory diseases, such as ankylosing spondylitis and rheumatoid arthritis (RA), suggested a potential role of TNF-α inhibition in the improvement of insulin sensitivity in non-diabetic rheumatic patients [41]. In a recent large observational study, in which 121,280 patients with RA or psoriasis were enrolled, the adjusted risk for developing T2D was lower for individuals starting a TNF inhibitor or hydroxychloroquine compared to the initiation of other nonbiologic disease-modifying antirheumatic drugs [42]. However, the administration of anti-TNF-α drugs in individuals with obesity and metabolic syndrome and patients with T2D was not found to improve insulin sensitivity, and consequently there is lingering uncertainty about the biological importance of this pathway in human insulin resistant states [43–45]. This lack of association could be the result of the autocrine/paracrine action of TNF-α in the adipose tissue, the small sample size of these studies, the dosing duration of anti-TNF-α therapy and the possible presence of more powerful determinants of insulin sensitivity in humans [43].

Interleukin 6

Adipose tissue produces approximately 15–35% of total human circulating levels of IL-6. Visceral adipose tissue produces three to four times more IL-6 than subcutaneous adipose tissue. IL-6 is mainly secreted from stromal vascular cells [46]. Elevated IL-6 plasma levels have been described in patients with T2D and especially in those who had features of insulin resistance [47]. These levels declined in parallel with weight loss in obese individuals undergoing bariatric surgery [48].
### Table I. Major molecules secreted from visceral fat that may induce insulin resistance: main results from preclinical and clinical studies

| Molecule | Preclinical and clinical studies (references) | Main results |
|----------|-----------------------------------------------|--------------|
|          | Cell cultures/animal models | Humans | |
| **TNF-α** | 34, 35, 39 | 40, 43–45 | Preclinical studies suggested that TNF-α decreased the expression of IR, IRS-1 and GLUT-4, promoting a serine phosphorylation of IRS-1. Its levels were associated with insulin resistance in humans. However, the administration of anti-TNF-α drugs in individuals with obesity, metabolic syndrome and patients with T2D was not found to improve insulin sensitivity |
| **IL-6** | 49, 50 | 47, 48 | IL-6 decreased the expression of IR, IRS-1 and GLUT-4, and inhibited the phosphorylation of IRS-1 in preclinical studies. Elevated IL-6 plasma levels have been described in patients with T2D, and especially in those with features of insulin resistance. Increased IL-6 levels were found during exercise |
| **IL-18** | 61 | 62 | IL-18 has an inhibitory effect on the insulin-induced Akt phosphorylation in human adipocytes. Studies in patients with T2D suggested that it was negatively related to fasting glucose levels and insulin activity |
| **Leptin** | 64, 65, 66, 72, 69 | 68, 70 | Leptin may enhance insulin sensitivity in several preclinical studies, while in some cell models it can promote an insulin resistant state. Leptin levels were also found to be higher in insulin-resistant than in insulin-sensitive subjects, serving as an endogenous response to an ambient insulin resistant state |
| **Resistin** | 75–80, 83 | 84, 85 | Resistin was found to cause insulin resistance in preclinical studies. However, several preclinical and clinical studies did not demonstrate any positive association |
| **RBP-4** | 88, 93 | 89, 90, 95–98 | RBP-4 plasma levels have been positively associated with the grade of insulin resistance in several preclinical and clinical studies. However, several studies in humans suggest that RBP-4 is not an independent determinant of insulin resistance |
| **MCP-1** | 100 | 101 | Preclinical and clinical studies suggested that MCP-1 stimulated insulin resistance in the liver and skeletal muscle, promoting an insulin resistant state |
| **PAI-1** | 104, 105 | 106, 107, 109 | PAI-1 promoted an insulin resistant state in preclinical studies. Increased levels were found in patients with T2D. It was suggested that PAI-1 was associated with increased cardiovascular morbidity and mortality |
| **A-SAA** | 113, 114, 117 | 115 | A-SAA promoted the down-regulation of phosphorysine INS-1 and GLUT-4 expression in preclinical studies. Circulating levels of A-SAA were found to be increased in subjects with obesity and patients with T2D in clinical studies |
| **ET-1** | 119, 120,121 | 123, 124 | ET-1 suppressed the intracellular activity of insulin by blocking the insulin-mediated phosphorylation of IRS-1 and IRS-2 in preclinical studies. ET-1 concentrations were found to be significantly elevated in patients with T2D and obese individuals with or without IGT |
| **AG-II** | 134, 135, 138 | 136 | Preclinical studies suggested that AG-II levels directly interfered with insulin signaling at the postreceptor level, modulating IRS protein phosphorylation and/or PI 3-kinase activity |
| **MIF** | 146 | 147 | Preclinical studies demonstrated that MIF reduced the tyrosine phosphorylation IRS-1 and its association with the p85 unit of the insulin pathway. Increased MIF levels were reported in obese and IGT subjects as well as in patients with T2D compared to controls |

TNF-α – Tumor necrosis factor-α, NEFAs – non-esterified fatty acids, T2D – type 2 diabetes, IGT – impaired glucose tolerance, IR – insulin receptor, IRS – insulin receptor substrate, GLUT-4 – glucose transporter 4, IL-6 – interleukin-6, IL-18 – interleukin-18, RBP-4 – retinol binding protein, MCP-1 – monocyte chemotactic protein-1, PAI-1 – plasminogen activator inhibitor-1, A-SAA – acute-phase serum amyloid A, ET-1 – endothelin-1, AG-II – angiotensin-II, MIF – macrophage migration inhibitory factor.
IL-6 may have a role in the development of insulin resistance in adipocytes and hepatocytes after decreasing the expression of IR, IRS-1 and GLUT-4. This phenomenon could be attributed to the upregulation of the suppressor of cytokine signaling-3 (SOCS-3) protein that inhibits the expression of IRs, promoting the prosedosomal degradation of IRS proteins [49]. IL-6 can also inhibit the phosphorylation of IRS-1 partly through SOCS-3 up-regulation [50]. Plasma IL-6 concentrations were also associated with an increase of NEFAs and C-reactive protein (CRP) levels [48].

However, IL-6 may promote glucose uptake and oxidation of NEFAs in animal and human skeletal muscle cells through the activation of AMPK [51]. Intracerebroventricular administration of IL-6 decreased body fat in rats, while increased IL-6 levels were also found during exercise [52, 53]. These data suggest that IL-6 can act both centrally and on peripheral tissues so as to influence glucose homeostasis and body weight in different ways [54]. Chronic increases of this cytokine in states of persistent inflammation may enhance insulin resistance, whereas acute transient increases may contribute to normal glucose homeostasis [50, 54].

### Interleukins 1, 18 and 8

Among the first cytokines reported to exert pro-inflammatory functions is IL-1 (α and β) [55]. IL-1β can impair insulin activity by reducing IRS-1 expression in adipocytes; it may have a potential role in the loss of pancreatic β-cell mass in T2D [55, 56]. IL-18 is another pro-inflammatory cytokine that plays an important role in joint inflammation and inflammatory bowel diseases [57]. Studies in IL-18−/− and IL-18R−/− mice suggested increased body weight accompanied by an insulin resistant state compared to wild type mice [58]. Increased IL-18 levels were found in patients with T2D [59].

IL-8 production in human adipocytes is stimulated by IL-1 and TNF-α, and has an important role in the recruitment of neutrophils, lymphocytes and monocytes [60]. It was recently shown to have an inhibitory effect on the insulin-induced Akt phosphorylation in human adipocytes [61]. IL-8 is mainly produced from visceral adipose tissue and...
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Leptin

Leptin, a 16-kDa protein, is solely secreted in a pulsatile fashion by adipose tissue and mainly by subcutaneous fat. It exerts its activities after binding to specific leptin receptors that are expressed in the brain and peripheral tissues. Leptin acts as a satiety signal on the hypothalamus and causes suppression of food intake, stimulating energy expenditure [63]. It may enhance insulin sensitivity in muscle cells through AMPK activation, inhibition of acetyl-coenzyme A carboxylase, and subsequent stimulation of fatty acid oxidation, through reduced malonyl CoA levels, leading to the reduction of intra-myocellular lipid levels [64]. It can also decrease visceral adiposity and intracellular hepatic triacylglycerol levels and prevent the lipotoxic effects of obesity on pancreatic β-cells [63, 64]. Several studies have reported that leptin can increase insulin sensitivity in normal and diabetic preclinical models; it may also correct the diabetic phenotype of ob/ob mice. These effects were achieved through the following: (i) An insulin-independent mechanism. (ii) An insulin-sensitizing mechanism. (iii) By reducing food intake and body weight [65, 66]. However, it must be noted that several other studies did not establish an association of leptin with enhanced cellular insulin activity [67].

The vast majority of obese individuals have high circulating leptin plasma levels, which are associated with increased concentration of inflammatory markers. Leptin levels were also found to be higher in insulin-resistant than in insulin-sensitive men regardless of the adiposity status; they may serve as an endogenous response to an ambient insulin resistant state [68, 69]. Obesity-related leptin resistance or tolerance and subsequent hypoleptinemia has also been described in pancreatic β-cells, leading to deregulation of the adipocyte-insulin axis. In turn, this was associated with higher insulin levels and stimulated adipogenesis, leading to a further increase in insulin secretion and β-cell dysfunction. Deleterious effects on various peripheral tissues including liver, vasculature and myocardium have also been suggested [70, 71]. Studies in obese mice suggested that leptin’s anorexigenic effects were attenuated, while its effect of increasing cardiovascular and renal sympathetic actions remained intact. This fact suggested the presence of selective leptin resistance that can partially explain the adverse cardiovascular actions of leptin in obesity and the promotion of an insulin resistant state [69].
At the cellular level leptin can promote insulin resistance through the serine phosphorylation of IRS-1 residues and the downregulation of IRS-2-associated P13-kinase activity in various cell models [72]. It may also induce expression of the SOCS-3 protein, which has a negative impact on IR and IRS protein function. Interestingly, SOCS-3 can induce leptin resistance in the hypothalamus, creating a vicious circle [73]. Currently the precise role of leptin in the pathogenesis of insulin resistance and T2D remains complex and challenging [67].

Resistin

Resistin is primarily secreted from mature adipocytes in rodents. In humans it is expressed primarily from adipose infiltrating macrophages [74]. Higher resistin mRNA expression was described in abdominal fat compared to thigh fat [75]. Resistin was found to decrease glucose transport in adipocyte cultures, causing severe hepatic insulin resistance in rodents [75, 76]. Absence of the resistin gene in rodents can activate the AMPK pathway and reduce the expression of genes that encode enzymes essential for hepatic gluconeogenesis. Furthermore, in vivo findings suggest that resistin can suppress muscle and liver AMPK activation [77, 78]. In rodents, circulating levels of resistin were positively associated with obesity and T2D.

Resistin promotes insulin resistance through up-regulation of the SOCS-3 pathway, the induction of Ser-636 phosphorylation of IRS-1 and the suppression of P13-kinase activation [79, 80]. It can stimulate the expression of TNF-α and IL-6 both in human and murine macrophages. It may also activate endothelial cells by promoting endothelin (ET-1) production and upregulating monocyte chemotactic protein (MCP)-1 secretion [81]. Impaired glucose transport in isolated cardiomyocytes was also suggested [82].

Lack of association among circulating resistin levels, BMI, insulin sensitivity and/or other metabolic parameters has been reported from several trials organized in adipocyte cells and mainly in humans; other groups suggested a positive association of resistin with obesity and T2D. This fact creates uncertainty on whether the role of adipocyte-derived rodent resistin in glucose metabolism can be translated to the biology of human resistin produced by macrophages [83–85]. However, a recent study organized in a humanized resistin mouse model has shown that human resistin is produced in response to inflammation and modulates glucose homeostasis, promoting an insulin resistant state [86].

Retinol binding protein (RBP)-4

RBP-4 was described as a rodent adipokine several years ago. It is mainly produced by hepatocytes and adipocyte cells [87]. Its possible role in humans was recently reported [87]. Insulin resistance was stimulated by the following (i) Enhanced expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase. (ii) By promoting downregulation of the insulin signaling pathway in skeletal muscle cells [88]. RBP-4 plasma levels have been positively associated with the grade of insulin resistance in specific GLUT-4 knockout mice, obese and IGT individuals and patients with T2D [88, 89]. Circulating levels of RBP-4 were associated with visceral fat and/or waist-to-hip ratio rather than BMI [89]. Increased levels of RBP-4 have also been associated with increased liver fat accumulation and hepatic insulin resistance [90]. Physical activity, lifestyle modification and gastric banding surgery were found to reduce RBP-4 levels and improved insulin sensitivity [91, 92]. A possible negative effect of RBP-4 in β-cell function, directly or by preventing the binding of transthyretin to its receptor, has been suggested [93]. However, it was recently postulated that the correlation of RBP-4 with insulin resistance could be attributed to the presence of renal insufficiency [94]. Recent evidence also suggests that RBP-4 is not an independent determinant of insulin resistance [95–98]. Hence, its role in human glucose metabolism is not well clarified [98].

Monocyte chemotactic protein (MCP)-1

Chemokine (C-C motif) ligand 2 (CCL2), known as MCP-1, is a potent chemoattractant molecule playing an essential role in the recruitment of monocytes/macrophages into the adipose tissue. It is produced from visceral fat in higher amounts compared to subcutaneous fat and mainly from vascular-stromal cells and hypertrophic adipocytes [99]. 3T3-L1 differentiated adipocytes treated with MCP-1 showed decreased insulin-stimulated glucose uptake and reduced expression of a variety of adipogenic genes [100]. Moreover, polymorphisms of the MCP-1 gene were positively associated with plasma MCP-1 levels and promoted an insulin resistant state [101]. MCP-1 was also shown to stimulate insulin resistance in the liver and skeletal muscle, suggesting a role as an endocrine hormone. However, MCP-1 may not be the only critical adipokine for macrophage recruitment in adipose tissue. Absence of MCP-1 in mice did not limit the obesity-associated infiltration of macrophages into the adipose tissue [102].

Plasminogen activator inhibitor-1 (PAI-1)

PAI-1 is an inhibitor of the fibrinolytic system. Visceral adipose tissue expresses more PAI-1 than subcutaneous fat. It is mainly produced from stromal-vascular cells rather than adipocytes [103]. Increased levels of PAI-1 have been associated
both with a pro-thrombotic and an insulin resistant state. PAI-1 levels decreased substantially after weight reduction [104, 105]. PAI-1 also affects WAT growth as it impairs pre-adipocyte migration and attachments to vibronectin [106].

The administration of a synthetic PAI-1 inhibitor in high-fat diet mice improved insulin sensitivity [107]. It was demonstrated that patients with T2D had three times higher PAI-1 plasma levels compared to controls [108]. PAI-1 could be a very early risk factor for the development of insulin resistance and eventually T2D [107]. It may also predict the formation of an atheromatous plaque [109]. It was found to be associated with increased cardiovascular morbidity and mortality [110].

**Acute-phase serum amyloid A (A-SAA)**

A-SAA is secreted from several body tissues including mature adipocytes [111]. Although the liver is considered to be the most important organ for A-SAA secretion, its expression was found to be higher in adipocytes than in hepatocytes under an insulin resistant state [112]. Down-regulation of phosphotyrosine IRS-1 and GLUT-4 expression by A-SAA was suggested to be responsible for the insulin resistant state observed in 3T3-L1 adipocytes [113]. Chemotaxis, infiltration of adipose tissue by macrophages, cytokine induction and the secretion of extracellular-matrix degrading proteases can also be induced by A-SAA [114, 115]. Circulating levels of A-SAA were found to be increased in obesity and T2D; they were correlated with the degree of insulin resistance [116, 117].

**Endothelin-1 (ET-1)**

ET-1 is currently considered as the most powerful natural vasoconstrictor. It is mainly produced from endothelial cells. It is also secreted from macrophages and VSMCs that surround adipocytes [118]. It mainly exerts its activity in a paracrine and autocrine fashion [119]. ET-1 may suppress the intracellular activity of insulin by blocking the insulin-mediated phosphorylation of IRS-1 and IRS-2 and the subsequent activation of the PI3-K pathway in VSMCs. In this way it aggravates insulin resistance [119, 120]. In vitro studies suggest that long-term adipocyte treatment with ET-1 promotes insulin signaling desensitization and decreases glucose transport [121]. ET-1 also inhibits the differentiation of preadipocytes to adipocytes [122]. Plasma ET-1 concentrations were found to be significantly elevated in insulin resistant states (T2D patients, obese individuals with or without IGT) compared to controls [123–126]. In a study organized in an obese population it was found that ET-1, either produced from adipose tissue or derived from the circulation, may have a major contribution in the selective resistance of visceral adipose tissue to the antilipolytic effect of insulin. It could also provide a vascular link between visceral fat accumulation and reduced insulin activity [127].

**Adipocyte renin-angiotensin system (RAS)**

Angiotensinogen and/or angiotensin peptides have been identified as secretory products of visceral fat in a higher rate than subcutaneous fat, early in the dynamic adipocyte development [128]. Angiotensin-II type 1 receptor (AT1R) and angiotensin-II type 2 receptor (AT2R) are also expressed in adipocyte cells [128, 129]. In vivo studies have suggested that the effects of angiotensin-II (AG-II) are mediated primarily through the AT1R receptor. The final result of these effects was the expansion of adipose tissue primarily through adipocyte hypertrophy [130, 131]. AG-II promotes an increased WAT mass since it has a local trophic factor effect early in the evolution of new adipocytes [132]. It also increases local oxidative stress in the adipose tissue [133].

Increased adipose tissue AG-II levels directly interfere with insulin signaling at the postreceptor level, modulating IRS protein phosphorylation and/or PI 3-kinase activity [134]. The administration of an AT1R antagonist contributed to an improvement of insulin activity in T2D mice. It also reduced plasma glucose levels and increased peroxisome proliferator-activated receptor γ (PPAR-γ) expression [135]. Interestingly, the hyperinsulinemia observed in an obese state can double the ability of AG-II to transactivate NF-κB. In this way it can stimulate multiple inflammatory pathways that block the insulin pathway and are involved in atherogenesis [136, 137]. Recently it was also shown that overexpression of angiotensinogen from WAT can cause glucose intolerance and may induce a systemic insulin resistant state through the reduction in muscle glucose uptake [138].

**Deregulated NO synthesis**

Of vital importance in maintaining vascular homeostasis is the production of NO. NO promotes smooth muscle relaxation and vasodilation. It also has important anti-thrombogenic and anti-inflammatory activities [139]. It suppresses VSMC proliferation, leukocyte adhesion and migration as well as platelet activation and adhesion [139]. NO is generated from the metabolism of l-arginine by the enzyme NOS. There are three isoforms of this enzyme: neuronal (nNOS), eNOS, and the inducible type (iNOS) [140].

Both eNOS and to a lesser extent iNOS are expressed in adipose tissue. In obese individuals eNOS expression was found to be increased in...
omental obesity compared to subcutaneous fat [141]. However, the asymmetric dimethylarginine (ADMA) produced in an obese state can act as an autocrine and/or paracrine inhibitor of eNOS. Hence it can deregulate a variety of adipose-related NO-mediated functions such as lipolysis, local blood flow, glucose metabolism and mitochondrial biogenesis [142]. ADMA has been associated with an insulin resistant state and CAD [142].

Recent evidence also suggested that the M1 macrophage phenotype found in visceral fat expresses iNOS, while the M2 macrophage phenotype seen in lean adipose tissue expresses the chitinase-like protein Ym1 arginase that inhibits iNOS activity [143]. M1 macrophage phenotype has been associated with a pro-inflammatory state compared to the “alternative activated” M2 macrophage phenotype [31]. Studies in mice demonstrated that visceral fat secreted increased amounts of iNOS, which resulted in increased nitrotyrosine levels in the liver, associated with insulin resistance [144]. It was also shown that chronic blockade of iNOS by N(G)-nitro-l-arginine methyl ester (L-NAME) in mice resulted in an improved insulin resistance [145]. Hence it can deregulate a variety of adipose-related NO-mediated functions such as lipolysis, local blood flow, glucose metabolism and mitochondrial biogenesis [142].

Adiponectin

Adiponectin is solely secreted from adipocytes and is a marker of adipocyte differentiation [152]. It is a 30-kDa adipocyte-derived vasoactive peptide that exerts its metabolic activities after binding to its cell-surface receptors (AdipoR1 and AdipoR2). AdipoR1 is expressed ubiquitously and mainly in skeletal muscle, while AdipoR2 is more abundant in hepatocytes. Full-length adiponectin synergizes with insulin in order to downregulate hepatic glucose production. The isolated globular domain of adiponectin also stimulates NEFA oxidation in skeletal muscle cells [153]. However, its strongest association is the improvement of hepatic insulin sensitivity and the suppression of hepatic glucose output [154, 155].

Circulating adiponectin is mainly found in three different isoforms: low molecular weight (LMW) trimers, middle molecular weight (MMW) multimers and high-molecular weight (HMW) (18mer) forms [156]. Most of its insulin-sensitizing effects are thought to be mediated through the HMW isoform [156]. The HMW isoform was reported to be superior compared to total adiponectin in predicting an insulin resistant state. Enlarged hypertrophic fat cells secrete reduced amounts of adiponectin. Weight loss increases its levels [157].

Adiponectin exerts its insulin-sensitizing effects through the following: (i) AMPK activation. In this way an increased rate of NEFA β-oxidation is achieved while the rate of lipogenesis is reduced. (ii) PPAR-α stimulation. Knockout of AdipoR2 in mice caused downregulation of PPAR-α signaling pathways and insulin resistance; concurrent inhibition of both AdipoR1 and AdipoR2 resulted in increased glucose intolerance and insulin resistance. (iii) Inhibition of the NF-κB pathway. (iv) A reduced rate of IRS-1 inhibitory serine phosphorylation and higher expression of GLUT-4. (v) Downregulation of the expression of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, leading to a reduction of neoglucogenesis [158–161]. Adiponectin can also improve glucose metabolism after stimulation of pancreatic insulin secretion both in vivo and in vitro [162].

Reduced adiponectin levels have been demonstrated in individuals with central obesity. Lower levels are also found in visceral compared to subcutaneous fat. Downregulation of adiponectin receptors was also shown in an insulin resistant state. Low levels of adiponectin led to an increased rate of TNF-α production from adipose tissue,
while both IL-6 and TNF-α can reduce the secretion of adiponectin [163]. Reduced adiponectin levels may predict the development of atherosclerosis in both diabetic patients and non-diabetic individuals. They have also been correlated with the development of insulin resistance, IGT and T2D in different ethnic groups [164–167]. Adiponectin levels vary among different populations, reflecting the ethnic differences in development of an insulin resistant state [168].

**Novel adipokines**

**Visfatin**

Visfatin, also called pre-B cell colony-enhancing factor 1 (PBEF1), is produced by the liver, muscles, human bone marrow and preferentially from visceral fat [169]. In vitro studies have suggested enhanced glucose uptake by myocytes and adipocytes. Inhibition of hepatocyte glucose release was also reported. This insulin-like activity of visfatin was suggested to be the result of IRS-1 and IRS-2 tyrosine phosphorylation and the subsequent activation of the PI 3-kinase pathway. It was also reported that visfatin exerted its insulin-mimetic effects by binding to the IR at a site distinct from insulin [170]. A possible role of visfatin in the regulation of β-cell function, as a systemic nicotinamide adenine dinucleotide (NAD) biosynthetic enzyme, was also demonstrated [171].

However, several studies in humans have reported an association of its levels with visceral fat and T2D, suggesting that visfatin may play a role in the pathogenesis of insulin resistance [172–174]. Moreover, visfatin levels were found to be reduced after exercise in patients with early onset T2D [175]. Recent evidence also indicates that visfatin levels may be associated with the severity of proteinuria and an advanced carotid atherosclerosis state in patients with T2D [176, 177]. Absence of an association between visfatin and insulin resistant state has been demonstrated in several studies performed both in rodents and humans [178–180].

**Vaspin**

Vaspin (visceral adipose tissue-derived serine protease inhibitor) is mainly produced from visceral adipose tissue [181]. It improves insulin sensitivity in preclinical models by inducing GLUT-4 expression [182]. When recombinant vaspin was tested in high fat and sucrose obese mice, improved glucose tolerance and insulin sensitivity were reported [183]. However, increased vaspin serum levels were associated with obesity and impaired insulin sensitivity; hyperglycemia was reported to amplify this association [184, 185]. It was also suggested that the upregulation of vaspin secretion from human adipose tissue could represent a compensatory mechanism in order to antagonize the actions of unknown proteases that are up-regulated in states of insulin resistance and/or IGT [183]. Metformin therapy in overweight women with polycystic ovary syndrome significantly decreased serum vaspin levels, possibly through the suppression of hepatic glucose production [186].

**Omentin**

Omentin is mainly produced from visceral fat compared to subcutaneous fat; stromal-vascular cells are the major source of its secretion. It improves insulin sensitivity in preclinical models by inducing GLUT-4 expression and Akt phosphorylation [187]. Omentin-1 is the major circulating form of omentin, while omentin-2 shares 83% amino acid identity with omentin/intelectin [188]. Omentin-1 was also identified in human epicardial fat [189]. Plasma levels of omentin-1 are inversely associated with waist circumference, BMI, leptin levels and insulin resistance. They are also positively correlated with adiponectin and high-density lipoprotein cholesterol (HDL-C) levels, and appear to improve insulin sensitivity in the adipocyte level [190]. Increased circulating omentin-1 levels were reported after weight loss; they were correlated with reduced BMI and improved insulin activity [191]. Absence of an association between circulating omentin levels and postprandial blood glucose levels was found [192].

**Apelin**

Apelin is produced similarly both in visceral and subcutaneous adipose tissue. Acute injection of apelin in normal mice resulted in a glucose-lowering effect that was correlated with improved glucose utilization in adipose tissue and skeletal muscle. In obese insulin resistant mice acute infusion of apelin also enhanced glucose utilization [193]. However, in patients with T2D both increased and decreased plasma apelin levels were observed compared to healthy controls [174, 194]. It was reported that apelin and apelin receptor expression both in mice and humans are regulated in a tissue-dependent manner and according to the severity of insulin resistance [195].

**Chemerin**

Chemerin is a chemoattractant protein expressed in the WAT, liver, pancreas and lung [196]. It has a described role in host defense, such as complement fibrinolysis, chemotraction and coagulation. Chemerin and its receptor, chemokine-like receptor 1 (CMKLR1, or ChemR23), have an important role in adipocyte differentiation [197]. Chemerin regulates the expression of adipocyte
genes encoding for molecules involved in lipid and glucose homeostasis (fatty acid synthase, GLUT-4, adiponectin) [198]. Improved insulin-stimulated glucose uptake through IRS-1 phosphorylation was demonstrated in 3T3-L1 adipocytes [199]. However, enhanced cross talk between adipose tissue and skeletal muscle can be induced by this protein; this, in turn, promotes a reduction of insulin activity [200]. Chemerin expression was found to be significantly higher in adipose tissue of diabetic and IGT Psammomys obesus compared with normal glucose-tolerant sand rats. Its levels did not differ significantly between T2D patients and normal individuals; however, in subjects with normal glucose tolerance, its levels were positively associated with BMI, blood pressure and triglyceride levels [197, 198].

NEFAs and the insulin pathway

Plasma NEFAs are elevated in an insulin-resistant state. Moreover, insulin resistance is improved when plasma NEFA levels are reduced [201]. Increased plasma NEFA levels are the result of three major pathophysiological events: (i) Insulin is a potent inhibitor of lipolysis by inhibiting the enzyme hormone-sensitive lipase. A reduction of insulin activity so as to suppress lipolysis from adipose tissue (mainly in hypertrophic adipocytes of visceral fat) in the post-prandial state is observed in the case of insulin resistance. Hence, it promotes the release of NEFAs to the circulation. (ii) NEFAs clearance is reduced. (iii) Elevated plasma NEFA levels further inhibit the anti-lipolytic effect of insulin; this in turn stimulates higher rates of NEFA release into the circulation [38, 202].

Fasting NEFA levels were inversely and independently associated with the risk of developing T2D [202]. Furthermore, T2D patients (lean and obese) are characterized by increased plasma NEFA levels during the whole day when compared with matched normoglycemic individuals, who are not normally suppressed after ingestion of a mixed meal or an oral glucose load [203]. It is also shown that the reported link between plasma NEFAs and T2D is strongest for the level of adiposity as opposed to insulin sensitivity and/or glycemic control, highlighting the close association of obesity with the development of T2D [204]. Increased cellular NEFA concentrations inhibit insulin secretion, stimulate gluconeogenesis and promote severe tissue insulin resistance [204, 205]. The main cellular mechanisms that underlie the effects of NEFAs on the insulin pathway are shown in Table III [38, 206–213].

Conclusions

During the last two decades a wealth of information has been accumulated regarding the structure and function of WAT. All this evidence has strongly improved our understanding of the pathophysiological mechanisms that underlie the development of insulin resistance and T2D [27, 31]. Continued accumulation of visceral fat contributes to adipocyte hypertrophy and increased infiltration with macrophages. Both adipocytes and macrophages secrete several adipokines, which create a complex network of factors, promoting, maintaining and exacerbating an insulin resistant state. Moreover, the increased cellular uptake of NEFAs without subsequent β-oxidation is exacerbated in an obese state, contributing to the accumulation of intermediate lipid metabolites; these metabolites cause defects in the insulin-signaling pathway [27, 214].

However, the following important observations must be taken into consideration: (i) There are still many discrepancies between data reported from rodents and humans regarding the roles of adipokines. This fact raises the possibility of species differences in the regulation of possible activities and cellular roles of adipokines. Data from studies in animal models may not be readily reflected in humans, possibly due to the variety and complexity of the cellular pathways involved. Hence, results from these studies must be interpreted with caution [34, 35, 39, 40–43, 54, 67, 75, 76, 83–85, 88, 89, 95–98, 172–174, 178–180, 183–185, 198]. (ii) The evidence for the systemic effects of some cytokines in humans is less well supported; some studies find no association, whereas others show an association between inflammatory cytokines and insulin activity. This discrepancy can be partially explained by the differences in the study populations and the methodological inter-study variation of the diagnostic methods used [215]. (iii) Questions also remain about the exact molecular mechanisms by which a number of these adipokines potentially exert their detrimental effects on insulin action. Numerous adipokines can act independently or in consonance. This complicated interplay along with their overlapping cellular activities creates uncertainties about their exact role and importance [216, 217]. (iv) Several adipokines are produced from non-adipose tissues, and thus it is not always straightforward to evaluate the specific contribution of WAT to the circulating levels of these factors. Whatever the case may be, it is absolutely essential that any potential relevance to human physiology is supported after a variety of distinct models report similar interpretations that are also described in humans; any inference on causality must be demonstrated in methodologically well-designed studies.

The integration of a lifestyle intervention program in order to improve glycemic control and cardiovascular risk factors is more than obligatory in...
patients with T2D [218, 219]. A large meta-analysis, in which approximately 10,000 participants were treated with either orlistat or placebo for at least 1 year, showed a mean placebo-subtracted weight loss of 2.9 kg [220]. Metformin therapy may facilitate a small or modest weight loss, reduce insulin requirements and improve hepatic biochemistry [221, 222]. The thorough understanding of the incretin system in the pathogenesis of T2D led to the evolution of incretin-based therapies. GLP-1 receptor (GLP-1R) agonists, namely exenatide and lixisenatide, have achieved significantly lower hemoglobin A1c (HbA1c) values that were associated with significant weight reduction in several clinical trials [223, 224]. GLP-1R agonists can be a very useful therapeutic tool in overweight or obese T2D patients with profound insulin resistance. A new class of drugs, the sodium glucose cotransporter 2 (SGLT-2) inhibitors, are under advanced investigation. These drugs exert their main activity in the proximal tubule by inhibiting glucose reabsorption, resulting in increased glucose excretion through the kidney; they have also been associated with significant weight loss [225]. Dapagliflozin has been approved by the European Medicines Agency (EMA) and canagliflozin in by the US Food and Drug Administration (FDA) for the treatment of patients with T2D [226]. Intestinal bypass procedures, mainly Roux-en-Y gastric bypass and biliopancreatic diversion with duodenal switch, have resulted not only in significant weight reduction but also in the remission of T2D within days or weeks after the procedure; they can also reduce any possible future renal and cardiovascular complications as well as cardiovascular mortality [227–230]. Further research is also needed in order to investigate whether leptin sensitizers can induce weight loss in leptin resistant or tolerant obese states, and whether they play a role in weight loss maintenance [231].

Table III. Main cellular mechanisms of NEFAs' inhibitory effect on the insulin pathway

| Pathophysiological mechanisms | Ref. |
|------------------------------|-----|
| (i) Enhanced uptake of NEFAs without subsequent β-oxidation. This in turn promotes the accumulation of lipid metabolites within cells. Defects in the insulin signaling pathway from increased intracellular levels of triacylglycerol intermediate metabolites (mainly long-chain fatty acyl Co-A, DAG and ceramides) have been reported in several studies. Intermediate metabolites mainly inhibit the insulin signaling pathway by increasing IRS-1 and IRS-2 serine/threonine phosphorylation. These effects are mediated through activation of multiple pro-inflammatory signaling pathways, such as PKC, JNK, IKK, IκB kinase/NF-κB and mTOR. In muscle cells, IRS-1 serine/threonine phosphorylation suppresses GLUT-4 translocation and consequently insulin-mediated glucose uptake is reduced. In hepatic cells, IRS-2 serine/threonine phosphorylation reduces the insulin stimulation of glycogen synthase activation and decreases the phosphorylation of FOXO, leading to increased hepatic gluconeogenesis. | 38, 206–208 |
| (ii) TLR-4 in macrophages is activated by saturated NEFAs and stimulates intracellular pathways with major importance in the induction of insulin resistance, such as NF-κB and JNK. It also induces the production of adipokines in primary adipocytes or adipocyte cell lines, such as MCP-1. MCP-1 can further enhance macrophage infiltration into the adipose tissue. | 207 |
| (iii) Stimulation of MMPs activity from NEFAs has been described. MMPs cause extracellular matrix degradation. Extracellular matrix degradation and remodelling is a crucial cellular event in order to allow adipocyte cells to increase their size and their pro-inflammatory potential → reduced tissue sensitivity to insulin. | 209 |
| (iv) NEFAs promote endothelial dysfunction. The latter is associated with an accelerated insulin resistant state since it alters the transcapillary passage of insulin to its target tissues. | 209, 210 |
| (v) Elevated plasma levels of NEFAs as well as their intermediate metabolites in skeletal muscle cells promote reduced expression of nuclear genes that encode enzymes involved in mitochondrial oxidative metabolism, such as PPAR-γ coactivator (PGC-1) → mitochondrial lipotoxicity, which contributes to an increased intramyocellular fat content and exacerbates the insulin resistant state. | 211, 212 |
| (vi) NEFAs can reduce the insulin-stimulated glucose transport after modulating glucose GLUT-4 gene transcription and mRNA stability. | 213 |
ed comorbid conditions, overweight and obesity [31, 232, 233].

Conflict of interest
The authors declare no conflict of interest.

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