
Pathophysiology of Diabetes Mellitus Type 2: Roles of Obesity, Insulin Resistance and β -Cell Dysfunction

Frank Thévenod

Department of Physiology and Pathophysiology, University of Witten/Herdecke, Witten, Germany

Abstract

The past two decades have seen an explosive increase in the number of people diagnosed with diabetes mellitus worldwide, particularly type 2 diabetes (T2D), which is found associated with modern lifestyle, abundant nutrient supply, reduced physical activity, and obesity. Actually, between 60 and 90% of cases of T2D now appear to be related to obesity. Numerous studies have shown that insulin resistance precedes the development of hyperglycemia in subjects that eventually develop T2D. However, it is increasingly being realized that T2D only develops in insulin-resistant subjects with the onset of β -cell dysfunction. It is therefore important to characterize the mechanisms of insulin resistance and subsequent pancreatic β -cell failure associated with obesity in order to better understand the pathophysiology of T2D and develop approaches to prevent T2D.

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Introduction

Diabetes mellitus (DM) encompasses a range of diseases that are characterized by elevation of the blood glucose level and lead to a reduced quality of life and life expectancy, with a greater risk of heart disease, stroke, peripheral neuropathy, renal disease, blindness and amputation. Depending on the etiology, DM can be divided into two principal forms, type 1 (T1D) and type 2 diabetes (T2D). T1D occurs in childhood and is due primarily to autoimmune-mediated destruction of pancreatic β -cell islets, resulting in absolute insulin deficiency. People with T1D must take exogenous insulin for survival to prevent the development of ketoacidosis. The frequency of T1D is low relative to T2D, which accounts for over 90% of cases globally. T2D is more prevalent in adulthood, though it is becoming more common in children

and adolescents. T2D is characterized by insulin resistance and/or abnormal insulin secretion. Individuals with T2D are not dependent on exogenous insulin, but may require it for control of blood glucose levels if this is not achieved with diet alone or with oral hypoglycemic agents.

DM has long been considered a disease of minor significance to world health, but is now developing into one of the main public health challenges for the 21st century. The past two decades have seen an explosive increase in the number of people diagnosed with DM worldwide. This DM epidemic relates particularly to T2D, which is taking place both in developed and developing countries. The global figure of people with DM is set to rise from the current estimate of 150 to 220 million in 2010, and 300 million in 2025 [1]. The direct healthcare costs of the disease are also considerable, and have been estimated at around 5% of the total annual expenditure on health in Western societies.

About 80% of T2D patients are overweight. In fact, obesity is a primary risk factor for 'metabolic' diseases, which include coronary heart disease, hypertension, but also T2D. Knowledge of adipocyte physiology is therefore crucial for a better understanding of the pathophysiological basis of obesity and T2D.

Physiology of Adipose Tissues

Adipose tissues are located throughout the body. Some of these depots are structural, providing mechanical support but contributing little to energy homeostasis. Other adipocytes exist in the skin as subcutaneous fat. Finally, several distinct depots are found within the body cavity, surrounding the heart and other organs, associated with the intestinal mesentery, and in the retroperitoneum. This visceral fat drains directly into the portal circulation and has been linked to morbidities, such as cardiovascular disease and T2D. Adipose tissues modulate energy balance by regulating both food intake and energy expenditure. They also have a considerable effect on glucose balance, which is mediated by endocrine (mainly through the synthesis and release of peptide hormones, the so-called 'adipokines') and non-endocrine mechanisms.

Among the endocrine factors, adipocyte-derived proteins with antidiabetic action include leptin, adiponectin, omentin and visfatin. For instance, in addition to its well-characterized role in energy balance, leptin reverses hyperglycemia by improving insulin sensitivity in muscles and the liver. According to the current view that intracellular lipids may contribute to insulin resistance, this occurs most likely by reducing intracellular lipid levels through a combination of direct activation of AMP-activated protein kinase (AMPK) and indirect actions mediated through central neural pathways [2]. Other factors tend to raise blood glucose, including resistin, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and retinol-binding protein 4 (RBP4). TNF- α is produced in macrophages and reduces insulin action [3]. IL-6 is produced by

adipocytes, and has insulin-resistance-promoting effects as well [4]. Such ‘adipocytokines’ can induce insulin resistance through several mechanisms, including c-Jun N-terminal kinase 1 (JNK1)-mediated serine phosphorylation of insulin receptor substrate-1 (IRS-1) (see below), I κ B kinase- β (IKK- β)-mediated nuclear factor- κ B (NF- κ B) activation, induction of suppressor of cytokine signaling 3 (SOCS3) and production of ROS [for review, see 5]. RBP4, a secreted member of the lipocalin superfamily, is regulated by the changes in adipocyte glucose transporter 4 (GLUT4) levels. Studies have shown that overexpression of RBP4 impairs hepatic and muscle insulin action, and *Rbp4*^{-/-} mice show enhanced insulin sensitivity [6]. Furthermore, high serum RBP4 levels are associated with insulin resistance in obese humans and patients with T2D [7]. The exact mechanisms how RBP4 impairs insulin action are, however, not clear.

Adipocytes also release non-esterified fatty acids (NEFAs) into the circulation, which may therefore be viewed as an adipocyte-derived secreted non-endocrine product. They are primarily released during fasting, i.e. when glucose is limiting, as a nutrient source for most organs. Circulating NEFAs reduce adipocyte and muscle glucose uptake, and also promote hepatic glucose output, consistent with insulin resistance. The net effect of these actions is to promote lipid burning as a fuel source in most tissues, while sparing carbohydrate for neurons and red blood cells, which depend on glucose as an energy source. Several mechanisms have been proposed to account for the effects of NEFAs on muscle, liver and adipose tissue, including protein kinase C (PKC) activation, oxidative stress, ceramide formation, and activation of Toll-like receptor 4 [for review, see 5, 8]. Because lipolysis in adipocytes is repressed by insulin, insulin resistance from any cause can lead to NEFA elevation, which, in turn, induces additional insulin resistance as part of a vicious cycle. β -Cells are also affected by NEFAs, depending in part on the duration of exposure; acutely, NEFAs induce insulin secretion (as after a meal), whereas chronic exposure to NEFAs causes a decrease in insulin secretion [9] (see below), which may involve lipotoxicity-induced apoptosis of islet cells [10] and/or induction of uncoupling protein-2 (UCP-2), which decreases mitochondrial membrane potential, ATP synthesis and insulin secretion [10, 11]. The ability to store large amounts of esterified lipid in a manner that is not toxic to the cell or the organism as a whole may therefore be one of the most critical physiological functions of adipocytes.

The Insulin Receptor: Transduction through Tyrosine Kinase

An understanding of insulin resistance requires knowledge of the mechanisms of insulin action in target tissues, such as liver, muscle and adipose tissue. The net responses to this hormone include short-term metabolic effects, such as a rapid increase in the uptake of glucose, and longer-term effects on cellular differentiation and growth [12]. The α -subunits of the insulin receptor are located extracellularly

and are the insulin-binding sites. Ligand binding promotes autophosphorylation of multiple tyrosine residues located in the cytoplasmic portions of β -subunits. This autophosphorylation facilitates binding of cytosolic substrate proteins, such as IRS-1. When phosphorylated, this substrate acts as a docking protein for proteins mediating insulin action. Although the insulin receptor becomes autophosphorylated on tyrosines and phosphorylates tyrosines of IRS-1, other mediators are phosphorylated predominantly on serine and threonine residues. An insulin second messenger, possibly a glycoinositol derivative that stimulates phosphoprotein phosphatases, may be released at the cell membrane to account for the short-term metabolic effects of insulin. The activated β -subunit also catalyzes the phosphorylation of other members of the IRS family, such as Shc and Cbl. Upon tyrosine phosphorylation, these proteins interact with other signaling molecules (such as p85, and Grb2-Sos and SHP-2) through their SH2 (Src-homolog-2) domains, which bind to a distinct sequence of amino acids surrounding a phosphotyrosine residue. Several diverse pathways are activated, and those include activation of phosphatidylinositol 3'-OH kinase (PI₃K), the small GTP-binding protein Ras, the mitogen-activated protein (MAP) kinase cascade, and the small GTP-binding protein TC10. Formation of the IRS-1/p85 complex activates PI3 kinase (class 1A), which transmits the major metabolic actions of insulin via downstream effectors such as phosphoinositide-dependent kinase 1 (PDK1), Akt and mTOR. The IRS-1/Grb2-Sos complex and SHP-2 transmit mitogenic signals through the activation of Ras to activate MAP kinase. Once activated via an exchange of GTP for GDP, TC10 promotes translocation of GLUT4 vesicles to the plasma membrane of muscle and fat cells, perhaps by stabilizing cortical actin filaments. These pathways coordinate the regulation of vesicle trafficking (incorporation of GLUT4 into the plasma membrane), protein synthesis, enzyme activation and inactivation, and gene expression [for further details, see 12, 13]. The net result of these diverse pathways is regulation of glucose, lipid, and protein metabolism as well as cell growth and differentiation.

Pathophysiology of Adipose Tissues: Obesity and Insulin Resistance

Lipid storage in adipose tissue represents excess energy consumption relative to energy expenditure, which in its pathological form has been coined 'obesity'. In recent years, overnutrition has reached epidemic proportions in developed as well as developing countries. This reflects recent lifestyle changes, however there is also a strong genetic component as well. While the biochemical mechanism(s) for this genetic predisposition are still under investigation, the genes that control appetite and regulate energy homeostasis are now better known. For example, adipocytes produce leptin (see above) that suppresses appetite and was initially considered a promising target for drug therapy. However, most overweight individuals overproduce leptin, and no more than 2–4% of the overweight population has defects in the leptin appetite

suppression pathway [14]. In contrast, genetic predisposition to obesity and/or T2D when excess calories are consumed is common in the population: for instance, polymorphisms in the peroxisome proliferator-activated receptor- γ_2 (PPAR- γ_2) gene may have a broad impact on the risk of obesity and insulin resistance. A minority of people is heterozygous for the Pro12Ala variant of PPAR- γ and is less likely to become overweight and less likely to develop DM when overweight than the majority of Pro homozygotes in the population [15].

One striking clinical feature of overweight individuals is a marked elevation of serum NEFAs, cholesterol, and triacylglycerols irrespective of the dietary intake of fat. Obesity is obviously associated with an increased number and/or size of adipose tissue cells. These cells overproduce hormones, such as leptin, and cytokines, such as TNF- α , some of which appear to cause cellular resistance to insulin [16]. At the same time, the lipid-laden adipocytes decrease synthesis of hormones, such as adiponectin, which appear to enhance insulin responsiveness. The insulin resistance in adipose tissue results in increased activity of the hormone-sensitive lipase, which is probably sufficient to explain the increase in circulating NEFAs [17]. The high circulating levels of NEFAs may also contribute to insulin resistance in the muscle and liver (see below). Initially, the pancreas maintains glycemic control by overproducing insulin. Thus, many obese individuals with apparently normal blood glucose control have a syndrome characterized by insulin resistance of the peripheral tissue and high concentrations of insulin in the circulation. This hyperinsulinemia appears to stimulate the sympathetic nervous system, leading to sodium and water retention and vasoconstriction, which increase blood pressure [18]. The excess NEFAs are carried to the liver and converted to triacylglycerol and cholesterol. Excess triacylglycerol and cholesterol are released as very-low-density lipoprotein particles, leading to higher circulating levels of both triacylglycerol and cholesterol. Eventually, the capacity of the pancreas to overproduce insulin declines which leads to higher fasting blood sugar levels and decreased glucose tolerance (see below).

Inflammation: A Process Associated with Obesity-Induced Insulin Resistance

Adipose tissue modulates metabolism by releasing NEFAs and glycerol, hormones – including leptin and adiponectin – and proinflammatory cytokines [19]. There is now clear evidence that obesity associated with or without T2D is an inflammatory state, consistent with the production of TNF- α and other cytokines by adipose tissue. Chronic inflammation of white adipose tissue characterized by macrophage infiltration is thought to contribute to insulin resistance associated with obesity, and in obesity, the production of many of these adipokines is increased. RBP4 induces insulin resistance through reduced phosphatidylinositol-3-OH kinase (PI₃K) signaling in muscle and enhanced expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase in the liver through a retinol-dependent mechanism. By contrast,

adiponectin acts as an insulin sensitizer, stimulating fatty acid oxidation in an AMPK and peroxisome proliferator-activated receptor- α (PPAR- α)-dependent manner [for review, see 5].

In obese animals and humans, bone-marrow-derived macrophages are recruited to the fat pad under the influence of proteins secreted by adipocytes, including macrophage chemoattractant protein-1 (MCP-1) [19]. In addition to adipocyte-derived factors, increased release of TNF- α , IL-6, MCP-1 and additional products of macrophages that populate adipose tissue might also have a role in the development of insulin resistance [20]. TNF- α and IL-6 act through classical receptor-mediated processes to stimulate both the c-Jun aminoterminal kinase (JNK) and the I κ B kinase- β (IKK- β)/nuclear factor- κ B (NF- κ B) pathways, resulting in upregulation of potential mediators of inflammation that can lead to insulin resistance. The adipokine MCP-1 and its receptor CCR2 may play a role in the recruitment of macrophages to white adipose tissue and in the initiation of an inflammatory response in mice. Thiazolidinediones, which are PPAR- γ agonists used clinically as insulin sensitizers, reduce MCP-1 levels and macrophage infiltration into adipose tissue [21]. Increased secretion of MCP-1 from adipocytes may thus trigger such macrophage recruitment, and the infiltrated cells may in turn secrete a variety of chemokines and other cytokines that further promote a local inflammatory response and affect gene expression in adipocytes, resulting in systemic insulin resistance.

NEFAs: A Critical Factor in the Development of Insulin Resistance

The amount of adipokines secreted from adipocytes is correlated with adipocyte size, i.e. with the amount of triglyceride stored in the cells. Such a relation implies that adipokines directly mediate insulin resistance associated with obesity. Given that the release of NEFAs also is correlated with adipocyte size and that an increase in the NEFA concentration in plasma is a common feature of insulin resistance, increased NEFA levels are also associated with the insulin resistance observed in obesity and T2D [22]. The passage of NEFAs across the plasma membrane and into the cell, where they are thought to exert their effects, is mediated in a specific manner by fatty acid transport protein 1 (FATP1), a transmembrane protein that enhances the cellular uptake of NEFAs. Interestingly, FATP1-deficient mice are protected from diet-induced obesity and insulin resistance [23]. The cytosol of cells also contains fatty acid-binding proteins (FABPs), which are thought to facilitate the utilization of lipids in metabolic pathways. Mice that lack both of two related adipocyte FABPs, aP2 and mall1, are also protected from diet-induced obesity and insulin resistance [24].

In fact, it appears that the release of NEFAs may be the single most critical factor in modulating insulin sensitivity. Insulin resistance develops within hours of an acute increase in plasma NEFA levels in humans [22]. Conversely, insulin-mediated glucose uptake and glucose tolerance improve with an acute decrease in NEFA levels