Obesity in the Pathophysiology of Diabetes

13

Juan Antonio Paniagua González and Antonio Vidal-Puig

Obesity as a Public Health Problem

Obesity and overweight states are characterized by an excessive accumulation of body fat. Depending on the amount of fat accumulated, but also on the individual's genetic and exposure to specific environmental factors, the obese patient can develop several health problems. The increase in the prevalence of obesity and associated complications is considered a major public health issue that affects all demographic groups, irrespective of age, sex, race, education, or economic level [1]. The World Health Organization (WHO) estimates that more than 1.9 billion adults (≥18 years old) were overweight, and of these over 600 million were obese, according to worldwide data registered in 2014 [2]. In the United States, obesity rates have been rising in both, adults and children in recent years [3–5]. The maintenance of a healthy weight, usually achieved between 18 and 25 years of age, requires a life-long sustained energy equilibrium between energy intake and energy expended, which is affected not only by diet but also age, stage of development, genetic makeup as well as epigenetic, level of nutritional education, as well as physical and psychosocial interactions [6, 7].

A useful tool to define a person as obese or underweight is the body mass index (BMI), estimated by the relationship between weight and height. The age-standardized death rate, from any reason, was generally lowest in subjects with a BMI of 22.5–24.9 kg/m^2 [8–10]. Moreover, deaths associated with high BMI are ranked fourth, behind deaths from hypertension, smoking, and unhealthy diets and ahead of deaths related to hyperglycemia, sedentary lifestyle, high salt intake, alcoholism, and high blood cholesterol levels [11]. Lastly, it is also of relevance that the association between nutrient intake and diseases, such as cancer, diabetes, cardiovascular disease (CVD) [12, 13], obesity, body fat distribution, hypertension, insulin resistance, and hyperglycemia, is well established [14–16].

Deaths from CVD, cancer, and diabetes account for approximately 65% of all deaths, and obesity, mainly abdominal adiposity, increases the risk of all these disorders. BMIs higher than 25 kg/m^2 have a direct relationship with mortality due to CVD [6, 17–21]. CVD accounts for about 38.5% of all deaths in United States. Of relevance, this figure has declined since the 1940s and 1960s [8], associated with several primary prevention activities, improved treatment for acute ischemic phase, and secondary intervention [22, 23].

Deaths from all cancers accounted for about 23% of the total [8]. As high BMI increases mortality from cancer in most specific sites [10, 24, 25], compared to people with normal weight, obesity could increase cancer incidence about 14% in men and 20% in women. People with BMI ≥ 40 kg/m^2 could increase risk of death from cancer up to 52% in men and 62% in women [26]. Higher circulating glucose levels, low-grade inflammatory state, increased oxidative stress, and an altered bioavailability of hormones, mainly insulin, estrogens, and androgens, could be implicated in the rise in current cancer rates obesity-related. Finally, during the 1990s, in the United States, there was an increase of diabetes prevalence to 61%, and of this ≈90% were type 2 diabetes (T2D), in parallel with increase in the obesity rates [27]. Diabetic patients have 2–4 times higher risk of incidents of CVD [28]. Recently, global mortality directly related to diabetes was observed to be 2.9 million, about 5.2% of all deaths. Of this 2–3% was observed in the poorest countries, and over 8% was in the United States, Canada, and the Middle East. In people aged 35–64, this rates increased from 6% to 27% [29].

In the United States, approximately 70% of T2D patients are overweight and obese, and over a period of 10 years, the risk of diabetes rose to 27% in people who gained 5 kg or

J. A. Paniagua González (✉)
Insulin Resistance, Metabolism and Adipose Tissue Unit, Maimonides Institute of Biomedical Research, University Hospital Reina Sofia, Córdoba, Spain

Endocrinology and Nutrition Services, University Hospital Reina Sofia, Cordoba, Spain

A. Vidal-Puig
Wellcome Trust MRC Institute Metabolic Science, MRC MDU, University of Cambridge, Cambridge, UK

Wellcome Trust Sanger Institute, Hinxton, UK

J. Rodriguez-Saldana (ed.), *The Diabetes Textbook*, https://doi.org/10.1007/978-3-030-11815-0_13

more [30]. Specifically, central obesity is strongly related with metabolic disorders associated with insulin resistance and diabetes [31, 32]. The current advice to prevent and treat T2D includes maintaining an ideal body weight (BMI < 27–30 kg/m^2), physical activity, limiting the intake of sugar and saturated fat, and increasing the consumption of mono- and PUFA, as well as whole grains and fiber [33–35].

Obesity: Measurements and Assessment

Measuring body weight provides a sense of the degree of obesity; however, a more accurate and comparable measure of obesity is obtained by relating body weight to height [36]. The BMI is calculated as the ratio between weight and height squared ratio and expressed as kg/m^2. Based on the BMI measurement, it can be discriminated low, normal weight, overweight, and obese states in adults. The WHO has standardized BMI as (1) lower than 18 kg/m^2 as low weight; (2) between 18 and 25 kg/m^2 is normal weight; (3) between 25 and 29.9 kg/m^2 is overweight; and (4) greater than or equal to 30 kg/m^2 is obese [37, 38]. However, the BMI does not provide information about body composition (fat-free muscle mass/fat mass) nor about the pattern of body fat distribution. Thus, a better measure of obesity that overcomes these limitations is the measurement of percentage of body fat (BF%), which relates total weight to the weight of the fat mass. Of course, this is more difficult to measure than the BMI limiting its daily clinical use, but several accurate methods exist [39]. Body composition can be estimated from anthropometric measurements of skinfold thicknesses in several anatomical regions [40]. In research, BF% is determined by hydrostatic weighing (body weight by immersion) as the gold standard [41]. Alternatively, the bioelectrical impedance analysis technique can directly estimates the amount of the fat-free mass (FFM) and indirectly the body fat by subtracting from total body weight [42]. Individuals with normal weight or overweight, but that also have a high BF%, exhibit a cardiovascular risk which is comparable to those with obesity estimated by BMI. Of note, it is observed that at the age of 20, a BMI equal to 30 kg/m^2 implies a 30% of BF%. However at the age of 60, the same BMI represents a 40% BF% in men and up to 40–50% BF% in older women [43].

BMI informs neither the location nor distribution of the excess body fat. Central obesity occurs when the excess of fat accumulates in the intra-abdominal area, even at the expense of a decreased fat accumulation in the peripheral adipose tissue. Several parameters can be used to measure central obesity. The most widely used requires measuring the waist circumference (WC) and hip ratio (HR) to create the waist-HR (WHR). Subjects having a large WC have increased mortality [44] despite having a BMI < 30. Thus, high-risk individuals are better identified by incorporating WC and WHR measurements to BMI [45]. The WC measurement of central obesity varies with race and is currently accepted as >88 cm in women and >102 cm in men in the United States [46]. Finally, the relationship of waist circumference to height (WHtR) can also be used to identify adults at high cardiometabolic risk [47–49]. All these parameters help also to predict the risk of metabolic diseases such as T2D [50].

In research intensive settings, more complex and accurate techniques are available, such as dual-energy X-ray absorptiometry (DEXA), computed tomography (CT), and magnetic resonance imaging (MRI). DEXA estimates body fat distribution by scanning arms, legs, and trunk [51, 52]. Differentiation between abdominal subcutaneous fat and intra-abdominal fat, which is composed of visceral adipose tissue (VAT) and intraperitoneal and retroperitoneal fat, is better seen by MRI and CT [53, 54]. Finally, single-voxel magnetic resonance spectroscopy is the gold standard for measuring ectopic fat, outside anatomically defined fat depots. Ectopic fat can be estimated after separating water and fat signals within each voxel (using software such as jMRUI) [55, 56].

Adipocyte and Adiposity Development

Types of Adipocytes and Differentiation

When describing fat depots, it is important to differentiate two types of well-differentiated adipose tissues, which have specific distribution and function and are referred to as white adipose tissue (WAT) and brown adipose tissue (BAT) (Fig. 13.1). The WAT main function is the deposit of surplus energy as triacylglycerol (fat), which could be mobilized and offered to other metabolically relevant organs through hormonal signaling. The WAT is designed to be plastic and expand. In fact, WAT accounts from 5% to 50% of human body weight. However, WAT is also a main source of endocrine signaling [57]. One of the key hormones is adiponectin, typically associated with metabolically "healthy" expansion of adipose tissue facilitating adipocyte lipid storage and consequently preventing ectopic lipid accumulation. Conversely, leptin prevents lipogenesis while facilitating lipolysis and fatty acid oxidation. These actions may be mediated centrally by activation of sympathetic efferent signals to both brown adipose tissue and WAT to induce lipolysis. Leptin has recently been suggested as therapy for individuals with generalized lipodystrophy, who frequently develop severe metabolic syndrome characterized by hepatic steatosis, insulin resistance, and diabetes mellitus.

Physiological expansion of WAT involves different degrees of hypertrophy and/or hyperplasia of adipocytes and active remodeling of vascular and mesenchymal stromal cells.

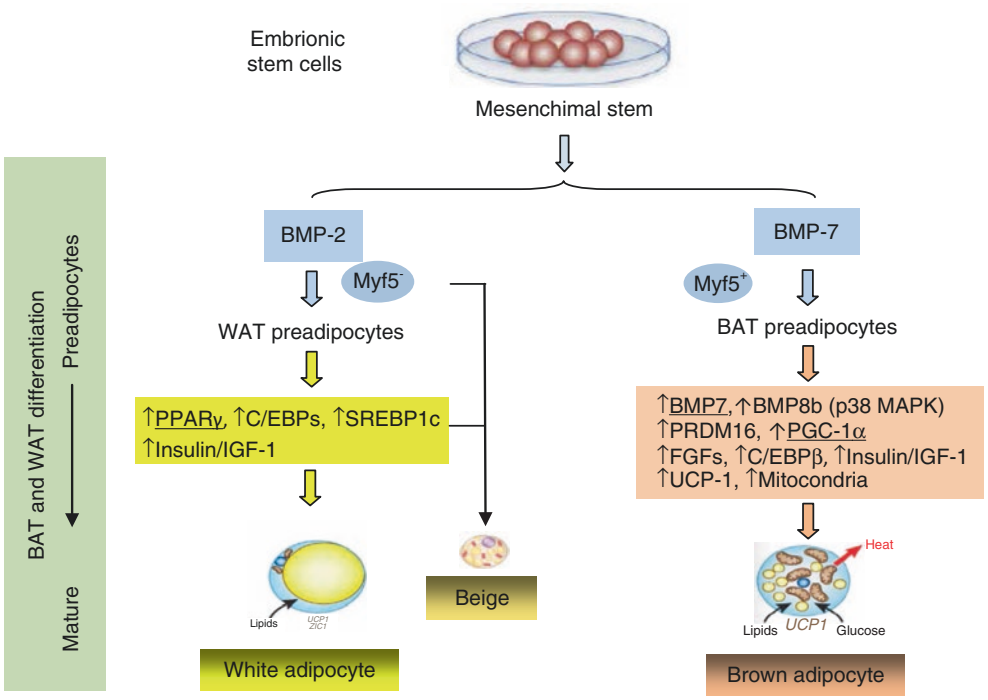

Fig. 13.1 Adipose tissue expands to store excess energy as fat and regulates fuel needs to other tissues. In WAT growth transcriptional factors such as the binding proteins CCAAT/enhancer-binding protein (C/EBP) and PPAR-γ are fundamental. Sterol regulatory element-binding transcription protein-1c (SREBP-1c) activates PPAR-γ expression [256] and mediates lipid biosynthesis by insulin [257]. Mature WAT is characterized by the expression of glucose transporter 4 (GLUT4) sensitive to insulin and enzymes like fatty acid synthase (FAS) and glycerol-2-phosphate dehydrogenase [258, 259]. During adipose tissue expansion, inappropriate vascular tissue development results in hypoxia, and death of adipocytes and macrophage infiltration is induced [260]. On the other hand, BAT derived from Myf5+ mesoderm progenitors shares a common origin with skeletal myoblasts [261]. The development of BAT requires that PRDM16 activates PPAR-γ coactivator (PGC-1α/β) or CtBPs and inhibits transcriptional factors that induce WAT [262, 263]. In addition, bone morphogenetic protein 7 (BMP-7) turns on a full program of brown adipogenesis involving induction of PRDM16 and PGC-1α and expression of UCP-1 which is a feature of brown cells [264]. Last, beige fat cells adapt functions, either like "WAT" when energy balance is exceeded or like "BAT" in response to stimuli similar to BAT activation. Today, research in identifying the main genes that control differentiation, development, and activation of BAT is highly active. (This work is licensed under a Creative Commons Attribution-NonCommercial (CC BY-NC 4.0) International License [231])

Also immune cells, endothelial cells, and undifferentiated or adipocyte precursor (AP) cells must also be coordinately developed [58]. Storage of excessive fat in WAT causes mechanical overload and contributes to increased risk of metabolic disorders. The repertoire of molecules secreted by adipocytes is not exhausted. Recently asprosin was described to be abundantly expressed in mature white adipocytes, accumulated in excess in the blood of humans with obesity and proportional to insulin levels, which has suggested asprosin levels may be associated with insulin resistance [59].

The role of BAT is thermogenesis contributing to energy expenditure and body weight regulation (Fig. 13.2) [60, 61]. In mammals, BAT is the primary site of thermogenesis in the absence of muscle contraction. BAT thermogenic function is mediated by the activation of a specific mitochondrial uncoupling protein 1 (UCP1) (Fig. 13.2). In humans, BAT function is particularly important for the control of body temperature after birth and in early childhood [62]. However, data from adipose tissue samples together with evidence provided by positron emission tomography coupled with computed tomography have established the existence of functionally active brown adipose tissue in adult humans [63–66]. Furthermore, some of these studies also relate the degree of activation of these sites with BAT and lower BMI, increased basal energy expenditure, and decreased onset of diabetes [67]. BAT in adult humans can be found in the cervical and supraclavicular [68] regions, depots identified as canonical BAT exhibiting similarities with the BAT in rodents. Lastly, recent studies have reported on secretory molecules from BAT, so-called batokines, which include fibroblast growth factor 21 (FGF21), neuregulin 4 (NRG4), vascular endothelial growth factor A (VEGFA), and bone morphogenetic protein 8B (BMP8B). These studies indicate that similarly to WAT, the BAT may also play a physiological role as an endocrine organ [69].

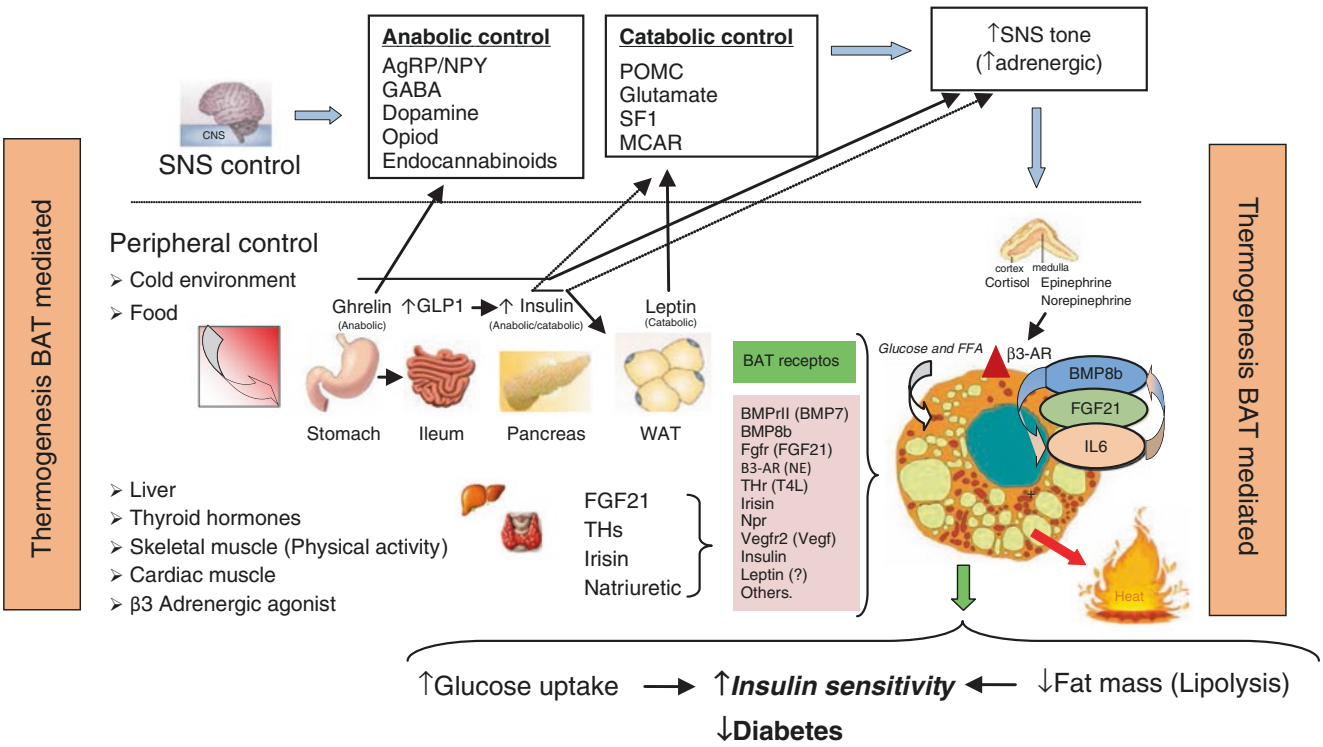

Fig. 13.2 *By contrast to WAT, brown adipose tissue* (BAT) was developed especially for energy expenditure (thermogenesis) mainly controlled by the SNS, which highly innervates brown fat cells. BAT is regulated in response to cold temperatures, hormones, and diet. BAT abundance and activation is highest in children and decreases with age. BAT activity decreases with BMI, body fat, and visceral obesity. Of note, BAT activity is lower in diabetics than nondiabetic subjects. Thyroid hormones play a key role in controlling BAT activation, such as the cold-induced deiodinates thyroxine (T4) to the more active T3. Norepinephrine binds to β-ARs inducing PGC1α and expression of UCP1. Whereas β1-AR mediates precursors of BAT proliferation, β3-AR plays a key role in the thermogenic function of BAT. Another signal, irisin hormone, released from muscle to fat tissue, mediates the beneficial effects of exercise reducing diet-induced obesity and improving insulin resistance. In addition, FGF21 is secreted by adipose tissue, liver, and skeletal muscle, through regulating lipolysis in WAT as well as increasing substrate utilization by increasing fatty acid oxidation in the liver. This actions may be mediated increasing activity of adiponectin. WAT white adipose tissue, BAT brown adipose tissue, PRDM16 PR domain containing 16, PPAR-γ peroxisome proliferator-activated receptor-γ, PGC-1α peroxisome proliferator-activated receptor γ coactivator 1α, SNS sympathetic nervous system, BMI body mass index, FGF21 fibroblast growth factor 21. (This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License [231])

On top of white and brown adipocytes, a third fat cell named beige/brite, which shares similarities with brown adipocytes, are found infiltrating skeletal muscle as well as in diverse areas of WAT [70]. Of note, beige cells are Myf5-positive cells, a classical feature of BAT, and appear dispersed in WAT [71]. The term "beige" describes their similar morphology with white adipocytes but the inducibility of features similar to brown adipocytes including UCP1 activity with β-adrenergic stimulation [72, 73]. There is also evidence that beige mature adipocytes can be interconvert between typical white and brown adipocytes, without the need for "de novo" cell differentiation from precursor cells [73]. A priori, this could mean that the rate of lipid storage or lipid oxidation could be adapted and adjusted in response to external stimuli such as a decrease or increase in temperature. Results from mice indicate that activated beige cells may contribute to improve carbohydrate metabolism and prevent/reverse fatty liver [74]. In any case, the physiological relevance of these cells in humans is far from being confirmed.

Effects of Hormones and Adipokines on Adipogenesis and Glucose Metabolism

Adipose tissue development and function are modulated by hormones, growth factors, secreted molecules by adipose tissue cells, nutritional factors, and pharmacological drugs (Fig. 13.2).

Hormones and Growth Factors

Insulin is key anabolic hormone that contributes to adipocyte differentiation and lipogenesis [75]. Brown preadipocyte determination is also regulated by insulin through a necdin-

E2F4 interaction that represses peroxisome proliferator-activated receptor-γ (PPAR-γ) transcription [76]. When in excess, hyperinsulinemia, either exogenously or endogenously, is a major enabler of adipose tissue expansion contributing to weight gain. Several molecules produced by cells from the adipose tissue, such as tumor necrosis factor alfa (TNF-α), leptin, and resistin, interact and inhibit insulin signaling on adipocytes.

Glucocorticoids and sexual hormones also affect the functionality and development of the adipose. For instance, the infusion of hydrocortisone increases levels of circulating free fatty acids (FFAs) by activating the mechanisms of lipolysis [77, 78]. Glucocorticoids promote adipogenesis by increasing the expression of both PPAR-γ transcription factors and C/EBPδ and decreasing the expression of pref-1 [79]. The adipocyte also has a complete arsenal of enzymes that regulate the metabolism of steroid sex hormones [80]. Glucocorticoids control activity of 11-β-hydroxysteroid dehydrogenase 1 and 2 (11 βHSD1 and 2) that can change the active form cortisol to inactive cortisone and vice versa [81]. Of note this enzyme is highly expressed in visceral adipose tissue which may contribute to regional redistribution of fat [82, 83]. Another key aspect related to adipose tissue distribution is in sex steroids. Body fat distribution is different in men and women, and adipose tissue has activity of either cytochrome P450-dependent aromatase or 17-β-hydroxysteroid dehydrogenase (17βHSD) enzymes that can modify the repertoire of steroids. Aromatase mainly regulate the rate of transformation of androgens into estrogens, while 17βHSD regulate the formation of a more active form of androgens. Of note, the ratio 17βHSD/aromatase in adipose tissue correlates directly with central obesity [80, 84].

Thyroid hormones are main contributors to global growth and development [85] by exerting an important role controlling energy metabolism and the function of the main metabolic organs such as the adipose tissue, liver, heart, skin tissue, or muscle [86, 87].

Growth hormone and insulin like growth factor 1 Growth hormone (GH) is critical for somatic growth but also has enormous influence of the regulation of body fat composition and distribution, through its lipolytic and anabolic effects [88].

Major Adipokines

Adipose tissue contributes to the metabolic control of energy substrates such as glucose and lipids and interacts with several hormonal systems. The molecules produced by adipose tissue (adipokines) act in many organs including adipose, muscle, and CNS. In obese and insulin-resistant patients, there are qualitative and quantitative changes in the repertoire of adipokines. For example, some adipokines increase (e.g., leptin, resistin), while others decrease (e.g., adiponectin) [89] (Figs. 13.2 and 13.3).

Leptin Leptin is secreted by adipocytes, establishing a negative feedback between the amount of adipose tissue and satiety centers in the brain [90, 91]. Leptin also serves as a sensor of energy availability enabling energy demands such as pregnancy and adaptation to starvation [92]. Leptin levels decrease after weight loss, enabling saving energy adaptive response involving low thyroid activity, sympathetic tone, and decreased basal energy expenditure [93]. Thus, treating leptin deficiency with recombinant leptin not only reduces food intake and body weight [94] but also reverses infertility, prevents lipodystrophy-associated metabolic complications, and reverses impaired glucose metabolism [95–98]. The leptin action appears to be facilitated by insulin, glucocorticoids, TNF-α, estrogens, and C/EBPα and is decreased by androgens, β3-adrenergic activity, GH, FFAs, and PPAR-γ agonist [99].

Leptin also plays an essential role in energy metabolism, by facilitating lipid mobilization and preventing ectopic fat accumulation (lipotoxicity syndrome) [100, 101]. Leptin facilitates lipid oxidation and by doing so can reduce excessive fatty acid accumulation in the liver, pancreas, heart, kidney, and muscle tissue (Figs. 13.2 and 13.3).

Adiponectin Adiponectin is produced in mature adipocytes and is more abundant in peripheral subcutaneous than visceral adipose tissue [102]. Adiponectin receptors are G protein-coupled highly expressed in the muscle (AdipoR1) and liver (AdipoR2) [103]. Through them adiponectin promotes lipid oxidation in skeletal muscle and the liver and reduces hepatic glucose production and postprandial hyperglycemia [104, 105] contributing to maintain metabolic homeostasis.

Adiponectin deficiency, as observed in obesity, plays a role in the development of insulin resistance and type 2 diabetes as suggested by the following: (a) Adiponectin levels have an inverse relationship with degree of obesity, insulin resistance, and T2D [106, 107], which is reversed by adiponectin treatment which results in improvement of IR [108]. (b) Adiponectin reduces FFA levels and is associated with improved lipid profile, glycemic control, and reduced inflammation in T2D patients [109]. (c) TNF-α plasma levels and its hepatic production are decreased by adiponectin treatment, which also improved hepatomegaly, steatosis, and ALT levels related with nonalcoholic fatty liver disease (NAFLD) [105] (Fig. 13.3). (d) The PPAR-γ agonists (thiazolidinediones, TZDs) redistribute lipids from central

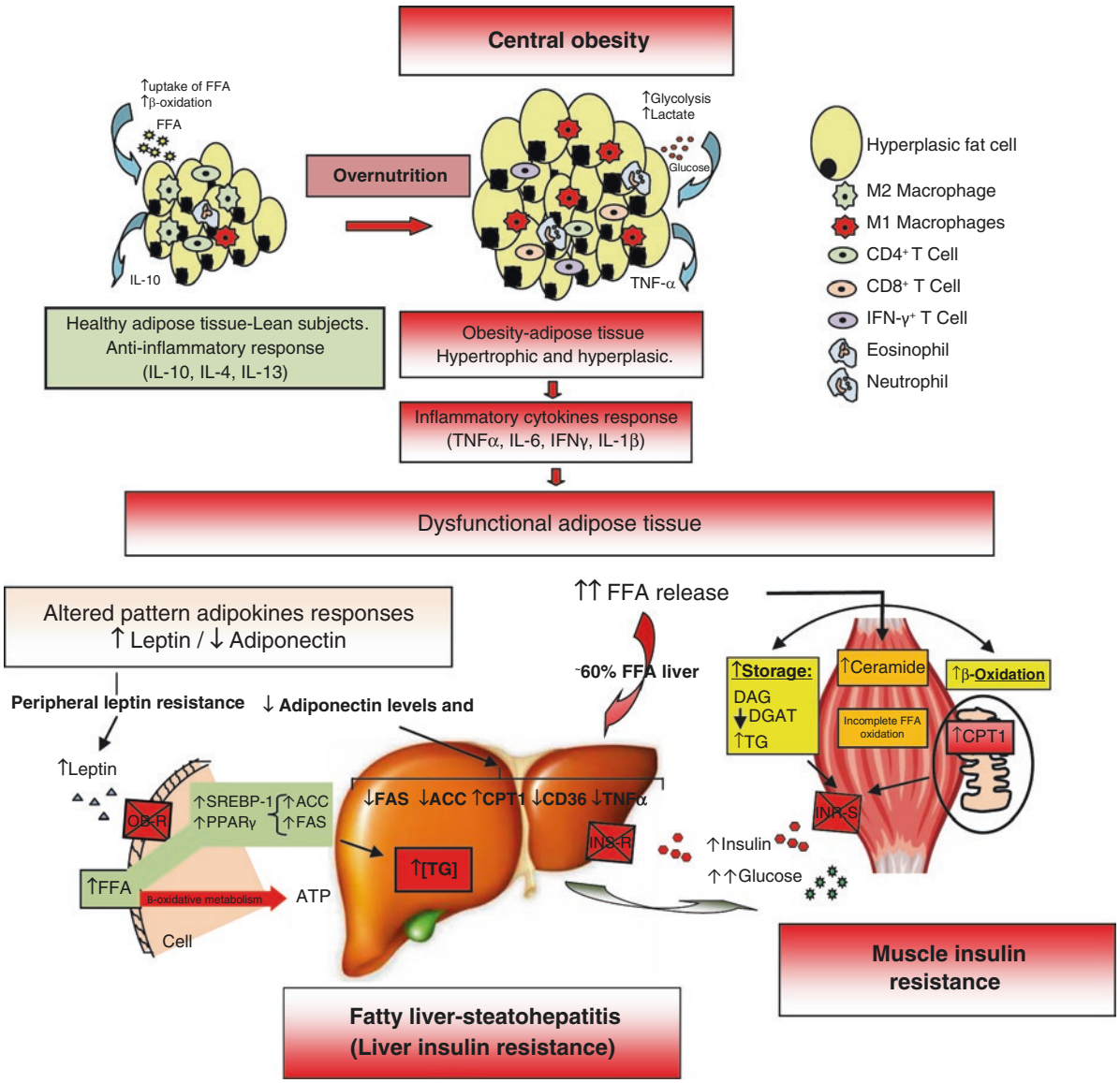

Fig. 13.3 Dysfunctional adipose tissue. When adipose tissue expands, it is slowly infiltrated by macrophages, and a low-grade chronic inflammatory state is developed [193, 265]. Several macrophage subtypes can be seen, which can be divided into pro-inflammatory M1 or alternatively activated M2 [266]. Adipocytes, macrophages, and immune T cells contribute to the production of inflammatory cytokines [127, 174, 193, 267]. The M1 macrophages are induced from precursor M0 macrophages by stimulation of type 1 T-helper (Th1) inflammatory cytokines like IFN-γ and TNF-α and lipopolysaccharide, whereas the M2 macrophages are induced by type 2 T-helper (Th2) cytokines such as IL-4 and IL-13. While adipose tissue of obese subjects shows mainly M1 macrophages, lean subjects have high levels of M2 macrophages. M2 macrophages are involved in remodeling and tissue repair through the action of IL-10, IL-1 receptor antagonist, and arginase-1, which result in better insulin sensitivity. Whereas M1 macrophages use glucose for energy, M2 macrophages activate the β-oxidation of fatty acids [266, 268]. Finally, M1 macrophages are a principal source of TNF-α which, by activating Wnt signaling and suppressing expression of PPAR-γ, interferes with the development and function of adipocyte and reduces the capacity to store triglycerides [269, 270]. Peripheral adipose tissue will expand to an equilibrium point, and when exceeded (inflexibility), glucose and lipid uptake decline, while insulin levels rise in order to maintain serum glucose within the normal range [271]. In addition, inflexibility is associated with early insulin resistance which increases lipolysis in adipose tissue, generating a redistribution of fats with systemic lipotoxic effects in the muscle, liver, β-cell, etc. (lipotoxicity). Furthermore, increased TNF-α and IL-6 levels are inversely related with peripheral and hepatic insulin-mediated glucose uptake [180]. The liver takes up excess released of FFA in serum to capacity by storing with triacylglycerol (TAG) and slowly fatty liver could be developed (NAFLD). Peripheral FFAs contribute ~60% of total TAG stored in the liver, whereas the de novo lipogenesis is ~26%, and ~15% is from food [230]. On the other hand, leptin levels rise with adipose expansion, while adiponectin levels tend to decrease. The elevated leptin levels should increase β-oxidation in non-adipose tissues, decreasing excess fatty acids in these cells. However, this action may be partially blocked by the anabolic effect of hyperinsulinemia, inducing a leptin system dysfunction (peripheral leptin resistance) [89]. In addition, adiponectin action improving peripheral glucose uptake and adiponectin protective action on liver fat accumulation are decreased [105]. Finally, both leptin and adiponectin seem to regulate the deposition of fat in insulin-sensitive tissues by increasing β-oxidation. IFN-γ interferon-γ, TNF-α tumor necrosis factor-α, IL interleukin, PPAR-γ peroxisome proliferator-activated receptor-γ, WAT white adipose tissue, FFA free fatty acids, NAFLD nonalcoholic fatty liver disease, CPT-1 carnitine palmitoyltransferase-1, FAS fatty acid synthase, ACC Acetyl-CoA carboxylase.

to peripheral depots and also increase adiponectin levels and improve lipid profile and insulin sensitivity while improving diabetes and NAFLD [110]. This suggests that maintaining normal levels of adiponectin may help in the treatment of early-stage diabetes. However, the relationship between adiponectin levels and cardiovascular disease is not well established [111].

Others Adipokines

Resistin has also been related to obesity, insulin resistance, and development of T2D. Blocking the action of resistin improves insulin sensitivity [112]; however, the significance of resistin in glucose metabolism in human still is inconclusive.

Visfatin is produced predominantly by abdominal adipose tissue and has been suggested to have insulin-mimetic actions [113, 114]. However, the importance of visfatin in glucose metabolism is still unclear [115].

Omentin-1 Obesity decreases both omentin plasma levels and omentin gene expression in visceral adiposity [116]. In obese women with polycystic ovary syndrome (PCOS), glucose and insulin levels were negatively related with omentin-1 levels, whereas metformin treatment increased serum omentin levels in parallel with improvements in insulin sensitivity and glycemic control [117, 118].

Obestatin is a hormone that opposes the effects of orexigenic effect of ghrelin. Obestatin decreases in subjects with diabetes and impaired glucose tolerance [119], and its receptors are downregulated in obesity-associated T2D [120].

Retinol-binding protein 4 Retinol-binding protein 4 (RBP4) is released from adipocytes and correlates with the degree of insulin resistance in obesity, T2D, and relatives of T2D patients [121–123]. The specific role of RBP4 in insulin resistance has not been determined.

Asprosin Is a 140-amino-acid polypeptide, recently described, abundantly secreted, and expressed in WAT. Levels of asprosin are increased in fasting situations in healthy humans. Asprosin acts on the liver stimulating hepatic glucose production. Asprosin administration induces a quick increase in plasma levels of glucose and insulin. Blocking asprosin actions might be beneficial for the treatment of type 2 diabetes mellitus [59].

Inflammatory Adipokines

TNF-α is a transmembrane protein released mostly by activated macrophages and also by other cell types including endothelial cells, adipocytes, etc. [124–126] (Fig. 13.3). Both TNF-α gene and its receptors are present in adipocytes and are expressed at higher levels in WAT [102]. TNF-α contributes to local and systemic inflammation, which limits the proliferation and differentiation of mature adipocytes. Increased release of TNF-α from adipose tissue contributes to the impairment of insulin action [127–129] and treatment with anti-TNF-α antibody led to improvement in glucose utilization in obese rats [127] at least. Similarly, obese mice genetically modified to ablate TNF-α had close to normal insulin sensitivity [129]. Moreover, weight reduction is associated with both improved insulin activity and decreased TNF-α gene expression [130]. The mechanism how TNF-α promotes insulin resistance may involve the decrease in the expression of PPAR-γ and target genes involved in lipid and glucose uptake [131, 132]. A link between fatty acid binding protein 4 (aP2), FFAs, and increased expression of TNF-α in obesity has been suggested [128]. Not only TNF-α but also interleukin-6 (IL-6) were both increased after nutritional fatty acid activation of Toll-like receptor 4 (TLR4) [133].

IL-6 is secreted by adipose tissue, T cells, and macrophages (Fig. 13.3). Adipocytes can produce IL-6, which is associated with C-reactive protein (CRP) levels and inflammatory states typically found in obese patients [134]. About 1/3 of the total concentration of IL-6 is produced in adipose tissue, mainly by visceral adipose tissue compared with peripheral adipose tissue [102]. It has been suggested that IL-6 levels are directly linked to obesity and insulin resistance [135] and to the inhibition of the activity of lipoprotein lipase (LPL) [136].

Chemokine molecules are potent chemoattractants of leucocytes and modulate the formation of reactive oxygen and cytokines. The chemokine molecule 5 (CXC ligand 5, CXCL5) is expressed at high levels by the macrophage of white adipose tissue [137]. Serum levels of CXCL5 are elevated in obese patients independently of their degree of insulin resistance above the levels observed in normal-weight subjects [137]. Furthermore CXCL5 serum levels are reduced after weight loss.

Fatty Acid Metabolism Effects on Adipogenesis and Glucose Metabolism

FFAs are energy-rich molecules fundamental regulators of metabolism. Excess calories ingested as fat, protein, and carbohydrates end up stored as triglycerides in white

adipocytes. FFAs are also essential constituents of the cell membrane, influencing its fluidity and the topology of receptors, transporters, and other membrane proteins. In addition, FFAs can have hormone-like actions and serve as ligands of nuclear receptors controlling gene expression [138]. Although food is the main source of essential fatty acids, de novo endogenous biosynthesis could supply nonessential fatty acids [139].

Both linoleic acid (ω-6 series) and linolenic acid (ω-3 series), have been related to decreased insulin resistance and CVD, must be included in the diet [140]. By contrast, excess saturated fatty acids and trans fats in the diet are associated with increased insulin resistance and risk of CVD [140].

LPL activity is increased by insulin and depends on apo CII and apo CIII being released by adipocytes. LPL is essential for FFA uptake from lipoproteins and storage [141]. In addition, cytoplasmic fatty acid-binding proteins (FABPs) facilitate intracellular transport and partition of FFA to specific compartments and functions [142]. FABPs link lipid metabolism, hormone action, and systemic energy homeostasis involving glucose metabolism [128].

De novo biosynthesis of saturated chain fatty acids is carried out mainly in the liver where acetyl-CoA is formed from pyruvate. Most de novo FFA are synthesized from acetyl-CoA and malonyl-CoA through two enzymatic steps, including acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). The ACC controls production of short fatty acids which are elongated until 16-carbon palmitic acid is formed by FAS (cytosol). Nearly all fatty acids required can be synthesized from palmitic acid by several steps of oxidation and elongation [143]. Finally, various enzymes which regulate the synthesis of triglycerides are also implicated in glucose metabolism [144]. Overexpression of diacylglycerol acyltransferase 1 (DGAT1) results in increased adipose tissue without affecting IS but increases the secretion of TNF-α [145]. A remaining question is whether de novo lipogenesis originated from fatty acids may have a specific fate or contribute to specific functions different from the pools of FAs generated from dietary nutrients.

Obesity Effects on Pathogenesis of Type 2 Diabetes

Type 2 diabetes mellitus (T2D) is characterized by hyperglycemia, insulin resistance, and inappropriately low secretion of insulin. The prevalence of T2D has increases in parallel with the increased prevalence of obesity [146] and sedentary lifestyle [147]. Pathogenesis of common forms of T2D is complex [148], requiring the combination of different degrees of insulin resistance and insulin deficiency [149]. In addition, insulin resistance and defects in insulin secretion can be determined via genetic and/or varying environmental factors, complexity that makes difficult to isolate a single cause in diabetic patients [150]. However, it is clear that the final development of diabetes requires beta cell failure as suggested by the fact that obese subjects do not necessarily develop T2D.

The potential molecular links between obesity and increased risk of T2D include exacerbated inflammatory response with excessive cytokine secretion (TNF-α and IL-6), insulin resistance, defects in fatty acid metabolism and lipotoxicity, mitochondrial dysfunction, and endoplasmic reticulum stress. However, weight loss is a central intervention working on most forms of prediabetes, because even modest weight loss improves glycemic control and reduces diabetes risk.

The risk of T2D and cardiovascular disease rises with the amount of body fat and more particularly when fat accumulates in central or abdominal depots [151]. Whether subcutaneous fat deposition is less pathogenic than visceral fat is quite likely but requires further investigation. In addition, the contribution of the subtypes of adipose tissue to glucose metabolism is important. For instance, increased level of brown adipose tissue may help to control carbohydrate metabolism and prevent or reverse obesity [63, 152].

Infiltration of immune cells in adipose tissue can alter its metabolic functions. Although the adipose tissue is not the cause of obesity per se, taking advantage of the specific functions of the repertoire of fat cell types and functional characteristics of the depots including the immune cells may help to uncouple obesity from its complications.

The main proposed mechanisms linking obesity to insulin resistance and T2D include (1) increased and altered secretion of adipokines (TNF-α, adiponectin, leptin, etc.) directly to inflammation and insulin resistance; (2) ectopic fat deposition, predominantly in the liver, skeletal muscle, and ß-cell, contribute to altered fat, insulin resistance, and glucose metabolism; and (3) mitochondrial dysfunction causing a bioenergetic cellular defect leading to decreased insulin sensitivity and defective pancreatic ß-cell function.

Effects of Fetal Develop on Adult Glucose Metabolism

The Nurses' Health Study (NHS) of over 69,000 women found an inverse relationship between birth weight and adult diabetes [153]. A meta-analysis with an adjusted odds ratio of diabetes of 0.80, 95% CI 0.72–0.89 for each 1 kg increase in birth weight confirmed this [154]. However, a higher birth weight (>4.0 kg) is also be associated with an increased risk of diabetes [155]. Lastly, a U-shaped relationship between birth weight and the development of T2D was found in a meta-analysis. Thus, high and low birth weight are associated with a similar increased risk of diabetes (ORs 1.36 and 1.47) [156] although not necessarily attributable to the same mechanisms.

Effect of Adult Obesity on Glucose Metabolism

After absorption in the intestine and after synthesis in the liver, triglycerides (TG) are transported in specialized lipoproteins [chylomicron and very low-density lipoprotein (VLDL)] to adipose and other tissues. Intracellular toxic accumulation of diacylglycerol and the input and output flows of FFA and acyl-CoA can be ameliorated by the formation and safe storage as TG [157]. Droplets containing TG are surrounded by a monolayer of phospholipids and proteins, e.g., perilipin (ADRP), which regulates lipid droplet formation, growth, and dissolution [158].

Obesity and Lipotoxicity Syndrome

The main function of the adipose tissue is fat storage. Adipose release of FAs and uptake into non-adipose tissues must be coupled matching demand and supply. For instance, in fasted state or during physical exercise, the lipolysis in adipose tissue is increased, a process that requires the coordination of suppression of plasma insulin and elevation of contrainsulin hormones (glucagon, cortisol, epinephrine, etc.). However, in obesity, it is quite normal to reach a prolonged overfeeding state, where fat load may exceed the functional storage capacity of the adipose tissue determining a state of metabolic inflexibility, where lipid uptake and mobilization is inefficient (inflexibility) (Fig. 13.4).

Another factor contributing to its functional defect is the adipocyte cell size. When adipocytes enlarge in an attempt to increase their capacity, they also become insulin resistant. This makes that the antilipolytic effect of insulin is reduced and that lipolysis of triglycerides from the adipose tissue as a whole increased and the bulk FFA release is increased. This leak of FFA and accumulation in plasma subsequently promotes insulin resistance in the muscle and liver [159] and also inhibits insulin secretion [160], ultimately causing β-cell apoptosis [161].

Among the most important factors controlling adipocyte capacity for storage and functional switch between storage and lipolysis, we identify the nuclear receptor PPAR-γ as a key transcription factor that controls the coupling between lipid storage and adipogenesis and lipolysis [162]. In addition, the direct role of leptin on adipose tissue functionality has been suggested. However, common forms of obesity are typically characterized by leptin resistance predominantly located at central hypothalamic action [163]. Leptin action central and/or peripherally appears to be implicated in processes that prevent lipotoxicity in non-adipose tissues through the regulation of β-oxidation mediated in part by its effects through peroxisome proliferator-activated receptor-α (PPAR-α) activity. This proxidative effect helps to minimize the metabolic burden of ectopic accumulation of lipids. Patients with insulin resistance syndrome have lower mRNA leptin abundance in peripheral adipocytes than IS patients (leptin resistance), even though insulin treatment acutely increases leptin levels [89, 164]. Another factor to consider is that a chronic increase of β-oxidation may contribute to oxidative stress and to generate inflammation, which may be potentially harmful [163].

Adiponectin, another adipose tissue derived hormone, also has a major role in improving insulin sensitivity, anti-inflammatory, anti-apoptotic, and pro-angiogenic effects that enhance whole body and adipose metabolic flexibility. Adiponectin action in adipose tissue improves both, the efficiency of the adipose tissue at regulating the releases of FFAs and increases the rate of FFA reesterification during the postprandial state [165]. However, the low serum adiponectin levels typically observed already in the early stages of insulin resistance are not sufficient to prevent the subsequent derail of adipose tissue function [89]. As part of the natural history toward the development of diabetes, there is progressive failure of the adipose tissue homeostatic mechanisms. When they are overwhelmed, lipids cannot be hold efficiently in the adipose tissue and accumulate in tissues that cannot store excess lipids such as the muscle, β-cells, liver, heart, and kidneys [101] without triggering metabolic toxic responses.

In addition with the leak of FAs, the dysfunctional adipose tissue also produces and releases an abnormal pattern of adipocytokine (e.g., decreased adiponectin and increases leptin, TNF-α and IL-6). This promotes an inflammatory state that further compromises the insulin sensitivity and functionality of the adipose tissue depot. Advancing in the natural history, the development of central obesity further exacerbates hyperinsulinemia and hyperglycemia, initially in the postprandial state and finally to global hyperglycemia. This phenotype is typically associated with hypertriglyceridemia, hypoalphalipoproteinemia, hypertension, and fatty liver (dysfunctional metabolism in the liver), a cluster of pathologies commonly diagnosed as metabolic syndrome (MetS) [166].

Pathogenesis of Obese Type 2 Diabetes

Obese T2D is typically associated with four clinical and metabolic defects: obesity, insulin resistance, dysfunction of β-cells, and increased hepatic endogenous glucose production [167]. However, the mechanisms by which these defects progress, the way they affect each other and contribute to the increase of glucose levels in obese T2D, are not fully elucidated. In a landmark longitudinal

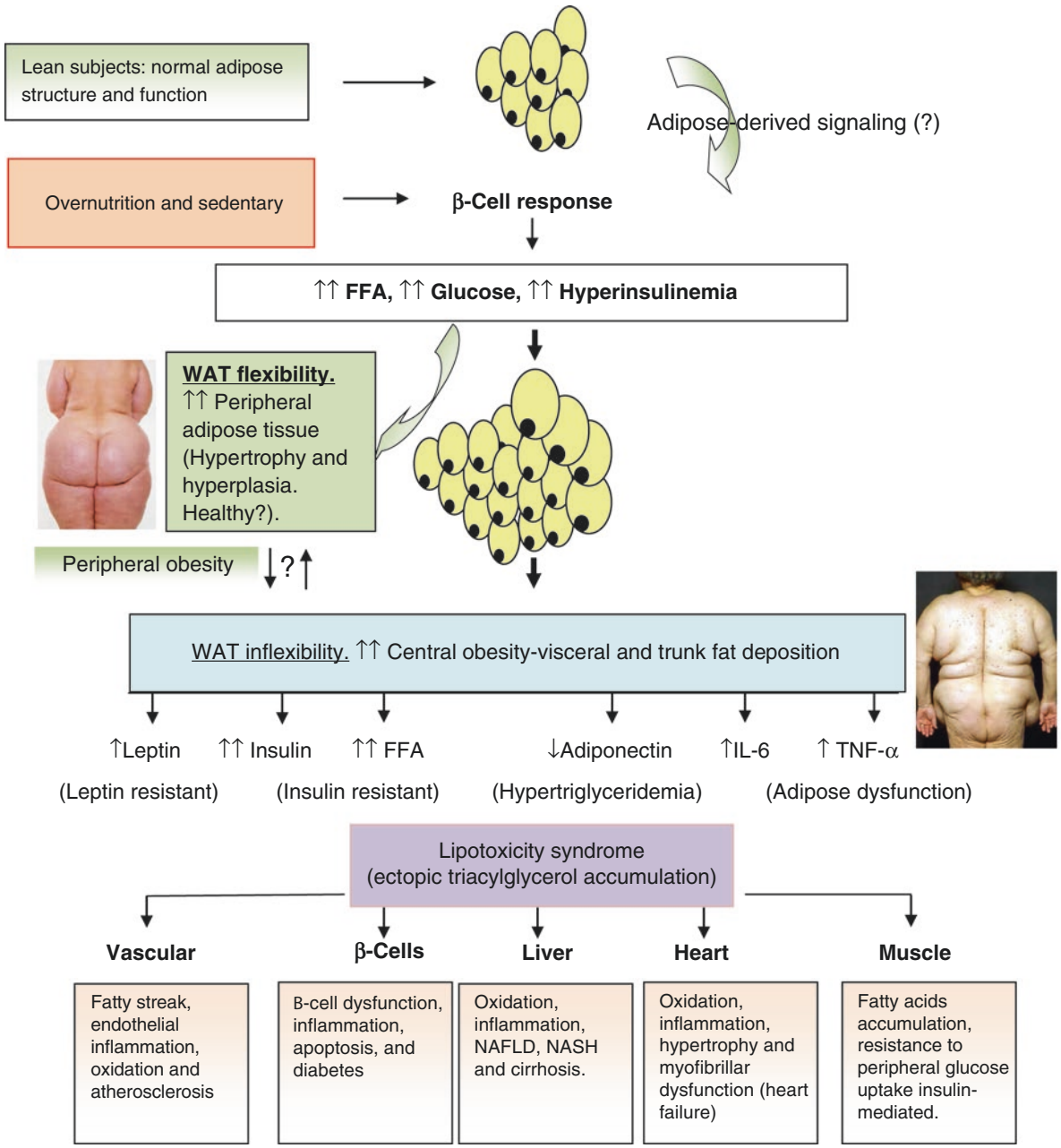

Fig. 13.4 Adipose tissue expandability and metabolic syndrome. After overeating with positive energy balance, adipose tissue increases its storage capacity, which is regulated by several factors. In individuals with a high capacity for storing fat, mainly when WAT is expanded (WAT flexibility), most, despite obesity developing, will remain normal, known as metabolically healthy obese (MHO). However, a low-grade chronic inflammatory response is frequently observed leading to dysfunctional adipose tissue [272]. Therefore, a pro-inflammatory milieu with elevation in IL-6 and mainly TNF-α, an altered adipokines profile with decreased adiponectin and increased leptin levels, will result in a dysfunctional adipose system. Increased release of cytokines and adipokines is related to insulin resistance, hyperglycemia, altered lipid profile, and cardiovascular diseases [89, 273, 274]. Insulin resistance is associated with the accumulation of lipids in non-adipose tissues such as muscle (lipotoxicity), due to increased lipolysis of fatty acids from adipose tissue. On the other hand, when the maximal storage capacity of adipose tissue is achieve, dysfunctional adipose tissue results, and redistribution of fat is initiated. Limitation in fat storage capacity could be necessary and even precedes the development of metabolic factors. Ectopic lipid accumulation in non-adipocyte cells causes lipotoxicity in these organs, including inflammation and apoptosis. Thus, lipotoxicity in β-cells could decrease β-cell mass (β-cell dysfunction) and can cause diabetes. Increased fat in the liver leads to NAFLD and nonalcoholic steatohepatitis (NASH) and could cause hepatic dysfunction, myocardial dysfunction in the heart, the endothelial fatty streak that could be a precursor of generalized arteriosclerosis, etc. The point at which adipose tissue begins to fail is probably influenced by genetic and epigenetic factors. However, the question is: Can storage capacity in WAT be enhanced to meet an increased demand? [275] One answer in humans is treatment with PPAR-γ agonists (TZDs) that transfer fat from central to peripheral deposits, improve lipid profile and insulin sensitivity, and reduce diabetes and NAFLD [110]. WAT white adipose tissue, MHO metabolically healthy obese, IL interleukin, TNF-α tumor necrosis factor-α, NAFLD nonalcoholic fatty liver disease, NASH nonalcoholic steatohepatitis, PPAR-γ peroxisome proliferator-activated receptor-γ, TZD thiazolidinedione. (This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License [231])

study of obese subjects with high incidence of T2D (Pima Indians of Arizona), peripheral insulin effect (euglycemic clamp), acute insulin response (AIR), and endogenous glucose production, in those whom glucose tolerance deteriorated from normal (NGT) to impaired (IGT) to T2D over 5.1 ± 1.4 years, were measured [167]. Patients who developed IGT typically presented increased body weight, decreased insulin sensitivity, and defective acute insulin secretion. In those who developed an open T2D, a greater increase in body weight, coupled with a more severe insulin resistance and deterioration of insulin secretion, and further increase of hepatic glucose production (HGP), was observed. By contrast, overweight patients who maintained normal glucose tolerance still gained weight associated despite decreased insulin-stimulated glucose disposal; however they maintained a robust insulin secretory response (AIR that was increased).

Another organ that is gaining relevance in metabolic failure associated with diabetes is the gut. The gastrointestinal tract should be considered as a large and specialized endocrine organ that releases two major incretin peptides: the glucagon-like peptide1 (GLP-1) by L-cells (distal small intestine) and glucose-dependent insulinotrophic peptide (GIP) by k-cells (early small intestine). GLP-1 and GIP jointly contribute to rise by 60–70% insulin released in response to a mixed meal [168]. In the context of the obese T2D patients, their β-cells generate resistance to GLP-1 and GIP [169]. Thus, despite their levels being normal or minimally reduced, their signaling in beta cells is dysfunctional. Moreover, GLP-1 also reduces glucagon releases by α-cells on the pancreas and reduces appetite. Finally, in these patients the GLP-1 resistance results in hyperglucagonemia and increased HGP and contributes to weight gain by promoting an orexigenic response [170].

The kidney is another point of metabolic control [171]. The kidney generates about 15–20% of the endogenous glucose production, mainly in fasting period, and is controlled by insulin function. But, the kidney in obese T2D is insulin resistant leading to an increase in its glucose production increases. Furthermore, the glucose filtered is efficiently reabsorbed by sodium glucose transporter 2 (SGLT2) (80–90%) and SGLT1 (10–20%). During early stages of hyperglycemia, this capacity of reabsorption is increased and contributes to maintain elevated glucose levels but also to retain sodium and water which may contribute to increase high blood pressure.

Contributing to the phenotype, it could be argued that as insulin and amylin, which is released together with the insulin, have anorectic signaling properties acting in hypothalamus, in obese T2D this signal of insulin is likely to be dysfunctional so that appetite is not suppressed which may contribute to overweight [172, 173].

Underlining Factors of Obesity-Induced Insulin Resistance

(a) *Inflammation and insulin resistance*

Long-time overfeeding and positive energy balance require adipocytes to increase their number and size. Excessive expansion of adipose tissue is associated with metabolic dysfunction, changes in adipokines, increased hypoxia, immune cell infiltration, and attempts to remodel, cell death, and apoptosis. Inflammation is part of an early homeostatic response aimed to repair of damaged tissues (Figs. 13.3 and 13.4).

Enlargement of adipose tissue is associated with secretion by adipocytes of monocyte chemoattractant protein (MCP)-1, which promotes monocyte infiltration in WAT and differentiation in adipose tissue macrophages (ATM) [174]. Moreover, adipocytes also induce the expression of the adhesion molecules ICAM-1 and platelet and endothelial cell adhesion molecule 1 (PECAM-1) on endothelial cells, which further attract monocytes [175]. The physiological role of this process is to facilitate the physiological remodeling of an expanding tissue. In obesity, failure to maintain the homeostasis of the organ results in uncontrolled inflammatory response generating a chronic low-grade inflammatory state. ATM contributes to the release of inflammatory factors. Of relevance macrophages share many adipocyte genes such as fatty acid-binding protein 4 (FABP4) and PPAR-γ, whereas adipocytes can express numerous macrophage factors such as TNF-α, IL-6, and MMPs [176]. Moreover, ATMs have been artificially classified as M1 pro-inflammatory and M2 anti-inflammatory macrophages on the basis of membrane markers. In obesity typically, there is an enrichment with a greater ratio of activated M1 than M2 macrophages [177, 178]. These pro-inflammatory M1 ATMs secrete pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, whereas M2 ATMs secrete anti-inflammatory cytokines including IL-10 and IL-1 receptor antagonist [178]. Of relevance the preferential type of ATM and degree of infiltration are linked with the progression of insulin resistance [179]. Hence, oversecretion of TNF-α from macrophages and to a lesser extent by adipocytes is a major characteristic of obesity and contributes to insulin resistance of obese humans [127, 180] (Fig. 13.3).

Inflammation of adipose tissue in obesity also involves infiltration of different T cells. Regulatory T cells (T_{reg}) represent 5–20% of the $CD4^+$ T cells and play a major role in controlling immune actions [181]. T_{reg} release anti-inflammatory cytokines, preventing macrophage infiltration and promoting a M2 macrophage phenotype [179]. Of relevance, with weight gain, a decrease in T_{regs} is observed [181], whereas there is an infiltration and activation of $CD8^+$ T cells that contribute to attract macrophages in the early stages of obesity [182].

Another relevant type of immune cells are the eosinophils, main contributors to IL-4-secretion, representing about 4–5% of cells in WAT. Macrophages are the main target of IL4 promoting an anti-inflammatory M2 phenotype which can improve glucose metabolism through preservation of M2 macrophages in WAT [183]. Lastly, neutrophils also seem to participate in the immune cell infiltration of the AT, contributing to obesity-induced insulin resistance [184].

Insulin sensitivity is affected by inflammation through various mechanisms. *TNF-α* inhibits insulin action by altering insulin receptor substrate 1 (IRS-1), though the activation of its p55 receptor [185]. In addition, TNF-α, FFA, ROS, and hypoxia activate IκBα kinase β (IKKβ) and c-Jun N-terminal kinase 1 (JNK1) in WAT and the liver inhibiting insulin activity by changing phosphorylation of IRS-1 [186, 187]. Furthermore, TNF-α also inhibits PPAR-γ function, with it impairs lipid synthesis and fat store in WAT. Moreover, inflammation increases plasma FFA levels through stimulation of lipolysis and reduction of TG synthesis, inducing insulin resistance in adipose tissue [188].

IL-1β activity requires two stress response signals. The first, necessary for production of pro-IL-1β, needs the activation of TLR4 (LPS, SFA, etc.) [189]. The second, which converts pro-IL-1β to active IL-1β, is controlled by the NOD-like receptor (NLRP)3-caspase 1 inflammasome complex [190]. Formation of NLRP3 inflammasome is induced by stressors that include FFAs, glucose, adenosine triphosphate (ATP), uric acid, ROS, etc. [191]. Thus, activation of the NLRP3 induces caspase-1 activity that converts pro-IL-1β to mature IL-1β. The major roles of NLRP3 inflammasome and caspase-1 activity in obesity-induced IR have been recently described [192].

Interleukin-6 is secreted by the WAT, skeletal muscle, and liver [193, 194]. Plasma IL-6 levels increase in overweight patients [195] in response to high levels of insulin and TNF-α. IL-6 inhibits insulin action through phosphorylation of IRS-1 [196]. In addition, raised IL-6 plasma levels are also associated with steatohepatitis and liver dysfunction [194]. However, IL-6 appears to stimulate insulin secretion by increasing the number of GLP-1 receptors in β-cells [197]. Thus, increased IL6 may contribute to the early increase of insulin secretion observed in obese patients. In addition, while elevated IL-6 secretion from WAT and the liver appears to have adverse metabolic effects, increased IL-6 secretion by skeletal muscle seems to be metabolically advantageous. In fact, physical inactivity has been shown to reduce skeletal muscle IL-6 expression and secretion [198]. The difference may be that whereas the increase in plasma IL-6 levels induced by exercise results from glycogen/MAPK activation and activation of anti-inflammatory levels of IL-1RA and IL-10 levels [199], the IL6 secretion from adipose and the liver is mediated by NF-κB, thus emphasizing the pleiotropic role of IL-6.

Finally, *interleukin-10* is an anti-inflammatory cytokine produced by monocytes, M2 ATMs, DCs, T cells, and B cells. Thus it is expected to play a favorable role in obesity-induced IR. Of relevance IL-10 is decreased in T2D [200], whereas weight loss increases IL-10 expression in WAT concurrent with diminished pro-inflammatory gene expression [201].

(b) *Mitochondrial dysfunction and obesity-induced insulin resistance*

Mitochondria is the main site for oxidation of fatty acids and glucose; thus its dysfunction may contribute to FFA and lipid accumulation and favor IR [202]. Mitochondrial biogenesis is activated by insulin and diminished in subjects with IR [203, 204]. In humans the existence of mitochondrial dysfunction in obese T2D who display lower NADH:O_2 oxidoreductase activity and reduced mitochondrial size than lean subjects has been observed [205]. Moreover, mitochondrial dysfunction in obese and insulin-resistant patients decreases lipid metabolism in muscle compared with lean control subjects [205–207]. Therefore, when mitochondria is exposed to excess lipids for β-oxidation, the oxidation of glucose may be impaired contributing to a state of insulin resistance. Furthermore, mitochondrial function improves after exercise training increasing uptake and oxidation of glucose in parallel with an improvement in insulin sensitivity [208]. In addition, molecular studies have found a decrease in peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), the key coactivator of mitochondrial biogenesis, and a decrease in phosphorylation pathways in muscle mitochondrial of T2D patients compared with control without diabetes [209, 210]. Thus, these studies have suggested the possibility of a genetic predisposition for mitochondrial dysfunction already observed in the early stages of insulin resistance and diabetes. Although a compensatory attempt to increase mitochondrial oxidative activity that could deal with the increased lipid supply in the short term has been shown [211], a sustained exposure to high-fat diet, prolonged for more than 4–6 weeks, may not be able to be compensated by increasing the mitochondrial activity leading to ectopic lipid accumulation and IR [212, 213]. However these observations are not consistently shown [214, 215]. It still unclear whether the observed defects in mitochondria function could be due primarily to a decrease in their number in muscle or secondary to metabolic defects within the mitochondria. It is known that insulin sensitivity improves after weight loss, an effect that does not require mitochondrial function to improve or even to change. Drugs which inhibit mitochondrial function and ATP production (TZDs, metformin, etc.) improve insulin sensitivity [216]. Lipid infusion-induced insulin resistance also enhances mitochondrial β-oxidation [217]. In nonobese sedentary humans after a period of overfeeding, IR was increased without changes in mitochondrial function [218]. Also muscle mitochondrial function was not distinctively impaired in obese and T2D compared with control subjects [218, 219]. Finally, there is some evidence that decreased mitochondrial function may induce insulin sensitivity, whereas an increase

mitochondria function is associated with insulin resistance in transgenic mice [214, 215]. Thus the relationship between mitochondria and insulin action remains complex and still not well established.

(c) *Oxidative stress and obesity-induced insulin resistance*

Mitochondria are an important source of superoxide generation in cells, having the greatest capacity for production in the electron transport chain (ETC). Under physiological conditions, mitochondrial superoxide contributes to mitochondrial function. Several studies have proposed a relationship between oxidative stress and IR. Lipid infusion increased levels of oxidative damage markers such as plasma thiobarbituric acid reactive substance (TBARS) and was associated with a decrease in insulin sensitivity [220]. A decrease in intracellular reduced glutathione (GSH) is associated with a decreased insulin sensitivity in T2D patients. In addition, infusion of GSH improved oxidative damage and insulin sensitivity [220, 221]. However, the physiological contribution of ROS to insulin sensitivity and metabolic response remains controversial, and several studies have been unable to reproduce consistently these observations [222, 223].

(d) *Endoplasmic reticulum stress and obesity-induced insulin resistance*

Endoplasmic reticulum (ER) is an important biosynthetic organelle that regulates many biological processes required for nutrient storage and metabolization. If the surplus of nutrients is greatly increased, synthesis, processing, and secretion of proteins may need to be increased, generating ER stress and dysfunction. Accumulation of unfolded or misfolded proteins is observed with ER stress [224]. ER stress is also induced by factors such as hyperglycemia, viral infections, hypoxia, and lipid overload or qualitative changes in membrane lipid composition [224]. ER stress has also been linked to the activation of chronic inflammation by activating JNK [225], raised oxidative stress, insulin resistance [226], and leptin resistance in obesity [227]. Moreover, amelioration of ER stress with drugs directly improves insulin sensitivity in obese mice and recently also observed in insulin-resistant obese patients [228]. However, the specific mechanisms and process by which ER stress induces insulin resistance in humans still remain to be fully elucidated.

(e) *Skeletal muscle glucose and lipid metabolism*

Adiponectin exerts direct effects in the skeletal muscle where it promotes fatty acid oxidation, decreases intramuscular lipid accumulation, reduces toxic deposit of ceramides, and results in the improvement of insulin sensitivity [57]. Leptin also may play an insulin sensitizing role in muscle through the CNS or through the leptin receptors which are highly expressed on muscle and participates on its growth. Leptin's effect seem more related to the enhancement in FFA oxidation and amelioration of lipid deposition in muscle mediated by AMPK activation [229].

(f) *Liver insulin resistance and hyperglycemia*

As the key organ regulator of lipid and glucose metabolism, the liver is commonly affected by ectopic lipid accumulation (Fig. 13.4). Fatty acids accumulation in the liver results from imbalance of different sources: dietary fat, increase in lipolysis from adipocytes, and from de novo hepatic lipogenesis, without excluding defects in oxidation and on lipoprotein assembly and secretion. High-fat diets have been shown to produce fatty liver, whereas low-fat/high-carbohydrate diets have been shown to produce hyperinsulinemia in the context of selective insulin resistance and stimulation of de novo lipogenesis via SREBP-1c. Thus, dietary composition can have a major effect by affecting the relative sources of fat in the liver. However, an overproduction of FFAs from adipose tissue in the context of obesity is probably the most likely source of the excess triglyceride accumulating in the liver [230].

When an inflammatory environment is established in the adipose tissue, the whole body lipid metabolism becomes altered, initiating postprandial hypertriglyceridemia, because the liver overproduction of VLDL is not removed in time and remains for longer in plasma (postprandial hyperlipidemia). Further, because lipolysis from peripheral adipose tissue is exacerbated, the interstitial content of FFAs increases, which can be taken up by the adjacent muscle cells (↓ IS) or again transferred into lipoproteins to the plasma and could be taken up by the liver (↑ VLDL production) and other organs (lipotoxicity).

The ectopic accumulation of fat in the liver has been strongly associated with both hepatic and adipose tissue insulin resistance, an almost universal finding in nonalcoholic fatty liver disease (NAFLD) [231, 232]. Thus, whereas insulin sensitivity is reduced by ~45–50% (whole glucose disposal), the ability of insulin to inhibit endogenous hepatic glucose production is also decreased. However, not all obese individuals necessarily develop metabolic complications, as some remain insulin sensitive and do not develop fatty liver [89].

On top of all these factors, the link between obesity and associated metabolic abnormalities seems to be better related to the topography, anatomical distribution, and/or the functional peculiarities of the adipose tissue, a phenomenon which seems to be more relevant in patients with relatively normal weight (Figs. 13.3 and 13.4). The mechanism(s) whereby increased visceral adiposity is associated with insulin resistance is unclear, but circulating hormones secreted from adipose tissue have been implicated in modulating insulin sensitivity. Importantly, adiponectin

receptors (AdipoR1 and AdipoR2) are expressed in the liver. Adiponectin is associated positively with insulin sensitivity and associated negatively with intra-abdominal and hepatic fat. Adiponectin stimulates glucose use and fatty acid oxidation in the liver by activating AMP-activated protein kinase (AMPK) and PPAR-α [57]. Moreover, adiponectin exerts a protective action on liver fat accumulation, favoring lipolysis by promoting the action of CPT-1 and enhancing fatty acid transport into mitochondria to undergo β-oxidation while preventing the action of FAS, ACO, and TNF-α and decreasing the expression and action of CD-36 protein that promotes the transport of fatty acids [105]. Adiponectin induces suppression of Sterol regulatory element-binding protein-1c (SREBP-1c) a key factor regulator of lipogenic gene expression in the liver. In addition, adiponectin lowers toxic hepatic ceramide accumulation by enhancing ceramidase activity. Recently it has emerged that FGF21, released by adipose tissue, liver, and skeletal muscle, increases adiponectin levels. Also treatment of T2D subjects with pioglitazone also increases adiponectin levels, and this has been associated with decreases in hepatic fat and correlated positively with hepatic and peripheral insulin sensitivity both pretreatment and posttreatment [233].

Leptin prevents de novo lipogenesis while activating β-oxidation of fatty acids in the liver and has anti-inflammatory effects on the liver. Leptin increases inclusion of triglycerides into VLDL enabling release of lipid from the liver. Clinical trial is currently ongoing to show the effect of leptin therapy for NAFLD.

With respect to the role of the inflammatory cytokines IL-6 and TNF-α, the plasma levels of these two inflammatory cytokines are increased in subjects with NAFLD and NASH [89]. Moreover, peripheral blood monocyte production of TNF-α and IL-6 is increased in subjects with NASH [234].

β-Cell Dysfunction in Obese T2D Subjects

In obese insulin-resistant subjects, the pancreatic β-cells homeostatically increase insulin secretion to maintain glucose levels. The mechanisms involved in this β-cell compensation are not well known but result in both increased generation of β-cells and enhanced β-cell functional responses (Fig. 13.5) [235, 236]. β-cell mass is increased in obese compared with lean subjects [237]. The signaling for compensatory β-cell mass expansion may include increased glucose and FFAs (probably the most important direct stimulus), insulin, and other growth factors [235]. Glucose is the natural stimulus to release storage granules and to synthesize insulin by β-cells. Glucose must enter β-cell by a special glucose transporter (GLUT2) increasing pyruvate and ATP/ADP ratio (glucose oxidation) which trigger insulin release (first phase) [238]. The maintenance of hyperglycemia stimulates specific β-cell glucokinase (GK) activity which forms glucose 6-P that increases insulin production (second phase) [238]. The expression of GK and GLT2 is directly associated with the differentiation of β-cells, and both are regulated by PDX1 [239].

In addition, FFAs are essential for amplification of glucose-stimulated insulin secretion (GSIS) and other nutrient and non-nutrient stimulus [240]. First, the binding of FFAs to FFAR1/GPR40 receptors increases intracellular Ca2+ necessary for insulin release and, second, through generation of malonyl-CoA (inhibits fatty acid oxidation), which increases intracellular LC-CoA and diacylglycerol levels (DAG), in the malonyl-CoA/LC-CoA pathway [240, 241]. In addition, nutrients stimulate L-cells in ileum, and higher fat content in food raises levels of glucagon-like peptide 1 (GLP-1) [242]. GLP-1 and FFAs can have synergistic actions increasing GSIS [243], which may also stimulate β-cell growth [244, 245]. However, the incretin effect gets progressively impaired during the transition from IGT to diabetes. In addition, obesity and glucose tolerance each attenuate the incretin effect on β-cell function and GLP-1 response [246]. Pancreatic cells are connected with the parasympathetic system increasing insulin secretion, and its hyperactivity may be involved in the growth of β-cells [247]. Histological studies of the pancreas from necropsies and surgery have supplied important data for our knowledge of pathogenesis of islet β-cell dysfunction in T2D [237, 248]. An important research focused on the pancreas obtained from necropsies analyzed the total number of beta cells (β-cell mass), the stage of beta cell in regeneration, and those in apoptosis (Fig. 13.5). One hundred and twenty-four pancreases in total from lean and obese subjects were investigated, both groups having normal glucose tolerance and T2D and the obese group having the addition of impaired fasting glucose (IFG) [237]. In patients with normal glucose tolerance, the study found that relative cell volume was increased in obese versus lean cases ($P = 0.05$) increasing the mechanism of neogenesis ($P < 0.05$). However, a decrease of 40% and 63% in β-cell mass in IFG and T2D obese patients compared with obese normal glucose tolerance subject was also observed. Lean T2D patients compared with lean normal glucose tolerance subjects had a reduction of 59% in β-cell mass. The reduction of β-cell mass is evident in patients with impaired fasting glucose suggesting that the loss of β-cell mass starts in the early stages. Finally, the study of mechanisms implicated in this loss of β-cell mass found no significant effect on β-cell neogenesis, but β-cell death by apoptosis was increased [237].

Underlying Mechanisms Implicated in β-Cell Failure in T2D

(a) *Glucotoxicity and glycation stress.* Insulin secretion is reduced during periods of hyperglycemia, while partial recovery of β-cell function is achieved after control of glucose levels in T2D patients. Glucotoxic mechanisms

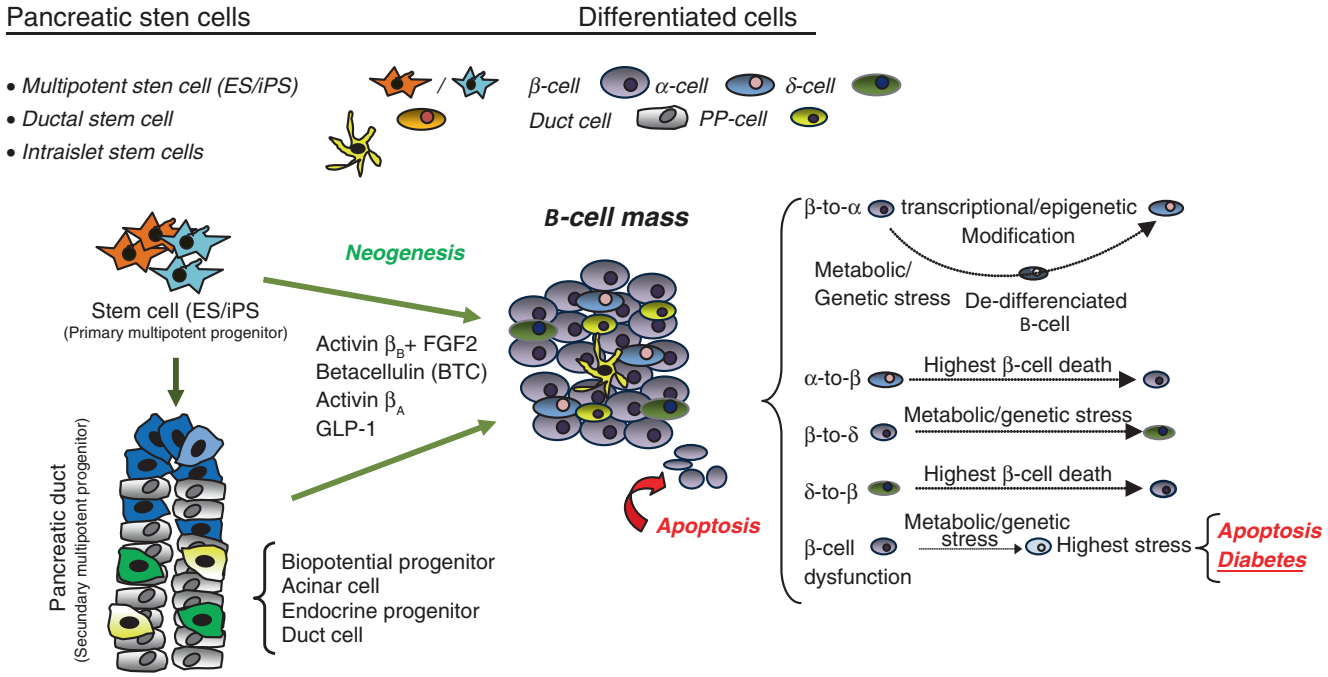

Fig. 13.5 Pancreatic β-cell failure appears as fundamental in the development of hyperglycemia in T2D, although insulin resistance may have been present for many years [276]. Insulin levels increase rapidly in relation with weight gain, probably associated with impaired insulin action; therefore hyperinsulinemia is frequently observed at diagnosis of T2D in obese subjects. However, only ~20% of obese subjects develop diabetes, while the remainder can maintain elevated insulin levels without hyperglycemia for many years. Thus, it appears that β-cell mass could progressively be reduced until it crosses a set point where insulin secretion is no longer sufficient to maintain the normal glycemic range in obese type 2 diabetic patients. Today, an increase in apoptosis of β-cells greater than a decrease in neogenesis is the most accepted cause for the loss of β-cell mass [237] (Fig. 13.5). β-Cell death can be increased by an accumulation of high toxic lipids, a human islet amyloid polypeptide, and finally by the generation of high levels of glucose in the type 2 diabetes with obesity. In addition, in obese individuals a high demand for insulin increases endoplasmic reticulum dysfunction (ER stress) and also hyperglycemia increases reactive oxygen species (oxidative stress) both contributing to apoptosis of β-cells. Thus, if β-cell mass is lower than 50%, the remaining β-cells try to increase their function in order to compensate, which produces chronic β-cell stress. Therefore, proinsulin levels are frequently increased early in developing T2D, probably due to ER stress of β-cells. In addition, proinsulin levels after hemiprancreatectomy determine the risk of developing diabetes, mainly in obese patients. Furthermore, the incretin effect is decreased in type 2 diabetes, affecting insulin secretion rates expressed as a percentage of insulin secretion. The incretin effect on total insulin secretion and β-cell glucose sensitivity and the GLP-1 response to oral glucose were significantly reduced in diabetes compared with NGT or IGT. Glucose tolerance and obesity inhibit the incretin effect independently [246]. In healthy subjects, infusion of physiological levels of GLP-1 increase insulin secretion. However, in patients with type 2 diabetes, physiological levels of GLP-1 had no effect on insulin release, whereas the infusion of GLP-1 at pharmacological levels (1 pmol/kg/min) increased just the "late-phase" (20–120 min) insulin response to levels similar to healthy subjects [277]. Furthermore, inflammatory pathways, such as increased interleukin-1β within islet β-cells, are involved in β-cell apoptosis in type 2 diabetes. Although the half-life and neogenesis rates of β-cells are difficult to establish in humans, it appears that β-cell can take several years to regenerate. However, interventions such as bariatric surgery can improve β-cell function in a few weeks in obese type 2 diabetes patients. In addition, β-cell function improved in obese T2D patients treated with a very-low-calorie diet (VLCD) weeks before insulin sensitivity was changed

implicated in β-cell damage include increased glucosamine pathway activity and glycation stress, raised oxidative stress, increased ER stress, activation of inflammatory, and toxic accumulation of islet amyloid polypeptide (IAPP) [249, 250].

(b) *Mitochondrial dysfunction and reactive oxygen species.* Increased surplus of glucose and FFAs raises its oxidation in mitochondria resulting in increased superoxide generation and production of uncoupling protein 2 (UCP2) in β-cell [251, 252].

(c) *Lipid effects on β-cell function.* An increased surplus of TG/FFA in β-cells induces glucose oxidation by which K+ATP channel pathway can be enhanced [243]. Thus, more than a direct lipotoxicity effect, elevated FFAs and hyperlipidemia can be a major signal for a flexible adaptation of β-cell mass to obese-induced insulin resistance [243]. However, the lipotoxicity effects of increased FFAs on β-cell can be seen more in combination with chronic hyperglycemia (glucolipotoxicity) [100, 241]. During hyperglycemia AMPK/malonyl-CoA signaling is stimulated, which slows down mitochondrial fat oxidation and promotes FFA accumulation in more complex lipids, some of which are lipotoxic [100, 241].

(d) *Islet β-cell exhaustion and ER stress.* The high requirement of insulin synthesis initiates mechanisms for compensating β-cell mass and generates high endoplasmic reticulum (ER) activity for the production of proinsulin. Continuous formation of proteins

including insulin results in stress and dysfunction of ER which affects the normal pattern of insulin secretion, a significant component of β-cell failure in T2D [253].

(e) *Differentiation of undifferentiated cells to pancreatic β-cells*

Hyperplasia, proliferation and neogenesis of pancreatic β-cells, may be adapted in relation to obese-induced insulin resistance and transitory β-cell damage. In humans pancreatic β-cell proliferation in pregnancy and T2D has not been observed. Therefore, similar to factors that induce multipotent stem cells (ES/iPS) to produce β-cells, we may be able to identify factors that inhibit pancreatic β-cell proliferation in various conditions. In humans, hyperglycemia progress is related with β-cell failure associated with a reduction of β-cell mass by increased apoptosis or dedifferentiation of β-cells during metabolic stressors such as is observed with obesity (Fig. 13.5).

Fate change between the different endocrine cells is observed under different conditions of stress. This may occur either directly or through a dedifferentiated state. Continued stress on the β-cell can lead to dedifferentiation that causes diabetes [254]. Future studies of some compounds that regulate endogenous stem-cell differentiation could lead to drugs that stimulate β-cells neogenesis [255].

Multiple Choice Questions

1. Talking about "Obesity: Measurements and Assessment," which one of the following statements is not correct?
   (a) Body mass index (BMI) is currently used to classify from low and normal weight to overweight and obese state in adults and is estimated by the weight/height squared ratio.
   (b) Deaths associated with a high BMI are ranked fourth behind deaths from hypertension, smoking, and unhealthy diets, and ahead of deaths related to hyperglycemia, sedentary lifestyle, high salt intake, alcoholism, and high blood cholesterol level.
   (c) Several clinical parameters can be used to estimate central obesity, with the most widely being waist circumference (WC), hip ratio (HR), and waist-HR (WHR).
   (d) In research, to measure obesity and body fat distribution, more complex and more accurate techniques are used, such as dual-energy X-ray absorptiometry (DEXA), computed tomography (CT), and magnetic resonance imaging (MRI).
   (e) In research the single-voxel magnetic resonance spectroscopy is the gold standard for measuring distribution of body fat.
2. With respect to the "Adipocyte and Adiposity Development," which one of the following statements is not true?
   (a) In humans there are two types of well-differentiated adipose tissues, which have different distributions and functions and are referred to as white adipose tissue (WAT) and brown adipose tissue (BAT).
   (b) The WAT is mainly related to the function of deposit of surplus energy as triacylglycerol, which could be mobilized and offered through hormonal signaling and has a tremendous ability to expand.
   (c) Adiponectin increases adipocyte lipid storage and prevents ectopic lipid accumulation. In addition, leptin decreases lipogenesis and increases lipolysis and fatty acid oxidation.
   (d) Thermogenic function of BAT is mediated by the activation of a specific mitochondrial uncoupling protein 1 (UCP1), where the saturation of the production of ATP is dissipated as heat. Therefore, activation of these sites with BAT decreases basal energy expenditure and increases onset of diabetes.
   (e) A third fat cell similar to brown adipocytes is also found infiltrating skeletal muscle and in different areas of WAT. This could mean that the rate of lipid storage or lipid oxidation could be adapted and adjusted.
3. Which characteristics or pleiotropic effects of hormones and adipokines on adipogenesis and glucose metabolism are not correct?
   (a) Adipocyte differentiation and lipogenesis require insulin receptors and insulin action.
   (b) The infusion of hydrocortisone increases levels of circulating free fatty acids (FFA) associated with the activation mechanisms of lipolysis.
   (c) The PPAR-γ agonists (thiazolidinediones, TZDs) increase fat central depots, also decrease adiponectin levels, worsen lipid profile and insulin sensitivity, and increase liver fat in NAFLD.
   (d) Leptin is secreted by fat cells, establishing a negative feedback between the amount of adipose tissue and satiety centers in the brain.
   (e) Adiponectin is produced in mature adipocytes and is higher in peripheral adipose tissue than visceral adipose tissue.
4. Talking about inflammatory adipokines all is true less one.
   (a) Both TNF-α gene and its receptors are present in adipocytes and at higher levels in WAT. Increased release of TNF-α from adipose tissue may play a role in the impairment of insulin action.
   (b) TNF-α increases the expression of PPAR-γ and increases expression of genes involved in lipid and glucose uptake.

(c) A fatty acid-binding protein (aP2) could be the link between FFA and increased expression of TNF-α in obesity.
(d) About 1/3 of the total concentration of IL-6 is produced in adipose tissue, mainly in visceral adipose tissue compared with peripheral adipose tissue.
(e) IL-6 levels are directly linked to obesity and insulin resistance and inhibit the activity of lipoprotein lipase (LPL).

5. Which of "Obesity Effects on Pathogenesis of Type 2 Diabetes" is not completely true?
(a) Type 2 diabetes mellitus (T2D), at least at the beginning, is characterized by hyperglycemia, insulin resistance, and impairment in insulin secretion. The prevalence has increased related with obesity and sedentary lifestyle but can arise genetic or varying environmental factors, which complicate finding the cause in diabetic patients.
(b) The risk of T2D and cardiovascular disease rises not only with the amount of body fat particularly increases when fat accumulation is in peripheral depots.
(c) Increased and altered secretion of adipokines in obesity (TNF-α, adiponectin, leptin, etc.) contributes to insulin resistance.
(d) Ectopic fat deposition, predominantly in the liver, skeletal muscle, and ß-cell, contributes to altered fat and glucose metabolism.
(e) Mitochondrial dysfunction and endoplasmic reticulum stress could be a link between obesity and diabetes, by decreasing insulin sensitivity and altering ß-cell function.

6. In relation to "Obesity and Lipotoxicity Syndrome," everything is true except one statement:
(a) Adipose tissue is the primary responsible for fat storage. Thus, a correctly functioning adipose tissue is necessary to maintain an adjusted delivery of surplus fuel to other tissues and nontoxic storage of lipids.
(b) When the adipocytes enlarge, it develops insulin resistance, and the antilipolytic effects of insulin is reduced. The increase of FFA in plasma results in more insulin resistance in muscle and liver, inhibits insulin secretion, and induces β-cell apoptosis.
(c) Leptin secretion decreases in parallel with fat accumulation and as a result adipose tissue expands. Leptin action appears to be implicated in processes that increase lipotoxicity in non-adipose tissues.
(d) Leptin regulates and increases β-oxidation through controlling peroxisome proliferator-activated receptor-α (PPAR-α) activity by minimizing ectopic accumulation of lipids.
(e) Adiponectin has a major role in improving insulin sensitivity, anti-inflammatory, anti-apoptotic, and pro-angiogenic effects that enhance the metabolic flexibility of adipose tissue.

7. In relation with "Pathogenesis of Obese Type 2 Diabetes," find out the statement that is not true:
(a) There are overweight subjects who maintain normal glucose tolerance. These can gain weight associated with insulin resistance (IR), but their acute insulin response (AIR) could be adjusted upward.
(b) The gastrointestinal tract is a large endocrine organ that releases two major incretin peptides. The glucagon-like peptide 1 (GLP-1) by L-cells (distal small intestine) and glucose-dependent insulinotrophic peptide (GIP) by k-cells (early small intestine) jointly rise by 60–70% insulin released in response to a mixed meal.
(c) GLP-1 reduces glucagon releases by α-cells on the pancreas and reduces appetite. In T2D patients, the GLP-1 resistance results in hyperglucagonemia and increased HGP and weight gain by eating.
(d) The kidney generates about a 15–20% of the endogenous glucose production, mainly in fasting period, and is controlled by insulin function. But, kidney in obese T2D is insulin resistant, and glucose production is decreased.
(e) The glucose filtered is reabsorbed by sodium glucose transporter 2 (SGLT2) (80–90%) and SGLT1 (10–20%). When hyperglycemia initiates, this capacity of reabsorption is increased and contributes to maintain elevated glucose levels and retention of sodium and water.

8. In relation with "β-Cell Dysfunction in Obese T2D Subjects," all are correct except one:
(a) In obese insulin-resistant subjects, pancreatic β-cells increase insulin secretion to maintain glucose levels. The mechanisms involved in this β-cell compensation are not well known but implicate both increased generation of β-cells and enhanced β-cell responses.
(b) The signaling for compensatory β-cell mass expansion includes increased glucose, while mainly FFAs, GLP-1, and insulin decrease β-cell mass increasing apoptosis.
(c) Glucose is the natural stimulus to release storage granules and to synthesize insulin by β-cells. Glucose must enter β-cell by a special glucose transporter (GLUT2) increasing pyruvate and ATP/ADP ratio (glucose oxidation) which trigger insulin release (first phase of insulin secretion).
(d) The maintenance of hyperglycemia stimulates specific β-cell glucokinase (GK) activity which

forms glucose 6-P that increases insulin production (second phase of insulin secretion).

(e) Pancreatic cells are connected by the parasympathetic system increasing insulin secretion, and its hyperactivity may be involved in the growth of β-cells.

9. Histological studies of the pancreas from necropsies and surgery have supplied important data for our knowledge of pathogenesis of islet β-cell dysfunction in T2D. Which of the following one is not true?
   (a) In patients with normal glucose tolerance has been found that relative cell volume is decreased in obese versus lean cases decreasing the mechanism of neogenesis.
   (b) A decrease of 40% and 63% in β-cell mass in IFG and T2D obese patients compared with obese normal glucose tolerance subject has been also observed.
   (c) Lean T2D patients compared with lean normal glucose tolerance subjects had a reduction of 59% in β-cell mass.
   (d) The reduction of β-cell mass is evident in patients with impaired fasting glucose suggesting that the loss of β-cell mass starts in the early stages.
   (e) The study of mechanisms implicated in this loss of β-cell mass found no significant effect on β-cell neogenesis, but β-cell death by apoptosis was increased.
10. Talking about "the underlying mechanisms involved in the failure of β-cells in T2D," point out the incorrect one:
   (a) Insulin secretion is reduced during periods of hyperglycemia, while partial recovery of β-cell function is achieved after control of glucose levels in T2D patients (glucotoxic mechanisms).
   (b) Glucotoxic mechanisms implicated in β-cell damage include increased glucosamine pathway activity and glycation stress, raised oxidative stress, and increased ER stress, activation of inflammatory, and toxic accumulation of islet amyloid polypeptide (IAPP).
   (c) An increased surplus of TG/FFA in β-cells induces glucose oxidation. Thus, more than a direct lipotoxicity effect, elevated FFAs and hyperlipidemia can be a major signal for a flexible adaptation of β-cell mass to obese-induced insulin resistance.
   (d) The lipotoxicity effects of increased FFAs on β-cell can be seen more in combination with chronic hyperglycemia (glucolipotoxicity).
   (e) Continuous formation of proteins, including insulin, results in stress and dysfunction of endoplasmic reticulum (ER) activity which not affects the normal pattern of insulin secretion in T2D.
11. The differentiation of undifferentiated cells to pancreatic β-cells plays a key role in the maintenance of the β-cell mass. Point out the incorrect of the following;
   (a) Hyperplasia, proliferation, and neogenesis of pancreatic β-cells may be adapted in relation to obese-induced insulin resistance and transitory β-cell damage.
   (b) In humans, hyperglycemia progress related with β-cell failure is associated with a reduction of β-cell mass by increased apoptosis and/or dedifferentiation of β-cells during metabolic stressors such as is observed with obesity.
   (c) Fate change of differentiation from multipotent stem cells (ES/iPS) between the different endocrine cells is observed under different conditions of stress.
   (d) Continued stress on the β-cell could lead to its dedifferentiation in an α-cell, which will not affect the normal pattern of insulin secretion in T2D.
   (e) Future studies of some compounds that regulate endogenous stem-cell differentiation could lead to drugs that stimulate β-cells neogenesis.

Correct Answers

1. (e) In research the single-voxel magnetic resonance spectroscopy is the gold standard for measuring distribution of body fat.
2. (d) Thermogenic function of BAT is mediated by the activation of a specific mitochondrial uncoupling protein 1 (UCP1), where the saturation of the production of ATP is dissipated as heat. Therefore, activation of these sites with BAT decreases basal energy expenditure and increases onset of diabetes.
3. (c) The PPAR-γ agonists (thiazolidinediones, TZDs) increase fat central depots, also decrease adiponectin levels, worsen lipid profile and insulin sensitivity, and increase liver fat in NAFLD.
4. (b) TNF-α increases the expression of PPAR-γ and increases expression of genes involved in lipid and glucose uptake.
5. (b) The risk of T2D and cardiovascular disease rises not only with the amount of body fat particularly increases when fat accumulation is in peripheral depots.
6. (c) Leptin secretion decreases in parallel with fat accumulation and as a result adipose tissue expands. Leptin action appears to be implicated in processes that increase lipotoxicity in non-adipose tissues.
7. (d) The kidney generates about a 15–20% of the endogenous glucose production, mainly in fasting period, and is controlled by insulin function. But, kidney

in obese T2D is insulin resistant, and glucose production is decreased.

8. (b) The signaling for compensatory β-cell mass expansion includes increased glucose, while mainly FFAs, GLP-1, and insulin decrease β-cell mass increasing apoptosis.
9. (a) In patients with normal glucose tolerance has been found that relative cell volume is decreased in obese versus lean cases decreasing the mechanism of neogenesis.
10. (e) Continuous formation of proteins, including insulin, results in stress and dysfunction of endoplasmic reticulum (ER) activity which not affects the normal pattern of insulin secretion in T2D.
11. (d) Continued stress on the β-cell could lead to its dedifferentiation in an α-cell, which will not affect the normal pattern of insulin secretion in T2D.

Author Contributions Paniagua JA was responsible for drafting and finalizing the manuscript. JAP and A V-P were responsible for final approval.

Conflict-of-Interest Statement The authors do not have potential conflict of interest.

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References

1. Berghofer A, Pischon T, Reinhold T, Apovian CM, Sharma AM, Willich SN. Obesity prevalence from a European perspective: a systematic review. BMC Public Health. 2008;8:200. https://doi.org/10.1186/1471-2458-8-200]. [PMID: 18533989 PMCID: 2441615].
2. World Health Organization. Obesity and overweight, http://www.who.int/mediacentre/factsheets/fs311/en/ WdU, 2016. UJ. Obesity and overweight, 2016. World Health Organization; 2016.
3. Engeland A, Bjorge T, Sogaard AJ, Tverdal A. Body mass index in adolescence in relation to total mortality: 32-year follow-up of 227,000 Norwegian boys and girls. Am J Epidemiol. 2003;157(6):517–23. [PMID: 12631541].
4. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. JAMA J Am Med Assoc. 2002;288(14):1723–7. [PMID: 12365955].
5. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. Int J Obes Relat Metab Disord: J Int Assoc Study Obes. 1998;22(1):39–47. [PMID: 9481598].
6. Kopelman PG. Obesity as a medical problem. Nature. 2000;404(6778):635–43. https://doi.org/10.1038/35007508. [PMID: 10766250].
7. Christakis NA, Fowler JH. The spread of obesity in a large social network over 32 years. New Engl J Med. 2007;357(4):370–9. https://doi.org/10.1056/NEJMsa066082. [PMID: 17652652].
8. Eyre H, Kahn R, Robertson RM, Committee AAACW. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. CA Cancer J Clin. 2004;54(4):190–207. [PMID: 15253917].
9. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, van der Schouw YT, Spencer E, Moons KG, Tjonneland A, Halkjaer J, Jensen MK, Stegger J, Clavel-Chapelon F, Boutron-Ruault MC, Chajes V, Linseisen J, Kaaks R, Trichopoulou A, Trichopoulos D, Bamia C, Sieri S, Palli D, Tumino R, Vineis P, Panico S, Peeters PH, May AM, Bueno-de-Mesquita HB, van Duijnhoven FJ, Hallmans G, Weinehall L, Manjer J, Hedblad B, Lund E, Agudo A, Arriola L, Barricarte A, Navarro C, Martinez C, Quiros JR, Key T, Bingham S, Khaw KT, Boffetta P, Jenab M, Ferrari P, Riboli E. General and abdominal adiposity and risk of death in Europe. N Engl J Med. 2008;359(20):2105–20. https://doi.org/10.1056/NEJMoa0801891. [PMID: 19005195].
10. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB, Beeson WL, Clipp SL, English DR, Folsom AR, Freedman DM, Giles G, Hakansson N, Henderson KD, Hoffman-Bolton J, Hoppin JA, Koenig KL, Lee IM, Linet MS, Park Y, Pocobelli G, Schatzkin A, Sesso HD, Weiderpass E, Willcox BJ, Wolk A, Zeleniuch-Jacquotte A, Willett WC, Thun MJ. Body-mass index and mortality among 1.46 million white adults. N Engl J Med. 2010;363(23):2211–9. https://doi.org/10.1056/NEJMoa1000367. [PMID: 21121834 PMCID: 3066051].
11. Ezzati M, Riboli E. Behavioral and dietary risk factors for noncommunicable diseases. N Engl J Med. 2013;369(10):954–64. https://doi.org/10.1056/NEJMra1203528. [PMID: 24004122].
12. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, D.C.: American Institute for Cancer Research; 2007.
13. Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: new insights. Circulation. 2011;123(24):2870–91. https://doi.org/10.1161/CIRCULATIONAHA.110.968735. [PMID: 21690503].
14. He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. BMJ. 2013;346:f1325. https://doi.org/10.1136/bmj.f1325. [PMID: 23558162].
15. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, Leboff MS, Rood JC, de Jonge L, Greenway FL, Loria CM, Obarzanek E, Williamson DA. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med. 2009;360(9):859–73. https://doi.org/10.1056/NEJMoa0804748. [PMID: 19246357 PMCID: 2763382].
16. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 2011;364(25):2392–404. https://doi.org/10.1056/NEJMoa1014296. [PMID: 21696306 PMCID: 3151731].
17. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, Hennekens CH, Speizer FE. Body weight and mortality among women. N Engl J Med. 1995;333(11):677–85. https://doi.org/10.1056/NEJM199509143331101. [PMID: 7637744].
18. Willett WC, Manson JE, Stampfer MJ, Colditz GA, Rosner B, Speizer FE. Hennekens CH. Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. JAMA. 1995;273(6):461–5. [PMID: 7654270].
19. Stevens J, Plankey MW, Williamson DF, Thun MJ, Rust PF, Palesch Y, O'Neil PM. The body mass index-mortality relationship in white and African American women. Obes Res. 1998;6(4):268–77. [PMID: 9688103].
20. Lindsted KD, Singh PN. Body mass and 26 y risk of mortality among men who never smoked: a re-analysis among men from the Adventist Mortality Study. Int J Obes Relat Metab Disord J Int Assoc Study Obes. 1998;22(6):544–8. [PMID: 9665675].
21. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults.

N Engl J Med. 1999;341(15):1097–105. https://doi.org/10.1056/NEJM199910073411501. [PMID: 10511607].
22. Association AH. Heart disease and stroke statistics. Update Dallas: American Heart Association; 2004.
23. Association AH. Heart disease and stroke statistics. Update Dallas: American Heart Association; 2003.
24. Lew EA, Garfinkel L. Variations in mortality by weight among 750,000 men and women. J Chronic Dis. 1979;32(8):563–76. [PMID: 468958].
25. Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, Martin-Hirsch P, Tsilidis KK. Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ. 2017;356:j477. https://doi.org/10.1136/bmj.j477. [PMID: 28246088].
26. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625–38. https://doi.org/10.1056/NEJMoa021423. [PMID: 12711737].
27. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS. Diabetes trends in the U.S.: 1990–1998. Diabetes Care. 2000;23(9):1278–83. [PMID: 10977060].
28. Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. Diabetes. 1999;48(5):937–42. [PMID: 10331395].
29. Roglic G, Unwin N, Bennett PH, Mathers C, Tuomilehto J, Nag S, Connolly V, King H. The burden of mortality attributable to diabetes: realistic estimates for the year 2000. Diabetes Care. 2005;28(9):2130–5. [PMID: 16123478].
30. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. Am J Epidemiol. 1997;146(3):214–22. [PMID: 9247005].
31. Landin K, Krotkiewski M, Smith U. Importance of obesity for the metabolic abnormalities associated with an abdominal fat distribution. Metab Clin Exp. 1989;38(6):572–6. [PMID: 2657328].
32. Peiris AN, Mueller RA, Smith GA, Struve MF, Kissebah AH. Splanchnic insulin metabolism in obesity. Influence of body fat distribution. J Clin Invest. 1986;78(6):1648–57. https://doi.org/10.1172/JCI112758. [PMID: 3537010 PMCID: 423938].
33. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001;345(11):790–7. https://doi.org/10.1056/NEJMoa010492. [PMID: 11556298].
34. American Diabetes A. (4) Foundations of care: education, nutrition, physical activity, smoking cessation, psychosocial care, and immunization. Diabetes Care. 2015;38(Suppl 1):S20–30. https://doi.org/10.2337/dc15-S007. [PMID: 25537702].
35. Kayikcioglu M, Ozdogan O. Nutrition and cardiovascular health: 2015 American Dietary Guidelines Advisory Report. Turk Kardiyoloji Dernegi arsivi: Turk Kardiyoloji Derneginin yayin organidir. 2015;43(8):667–72. https://doi.org/10.5543/tkda.2015.80963. [PMID: 26717326].
36. Magnusson I, Rothman DL, Katz LD, Shulman RG, Shulman GI. Increased rate of gluconeogenesis in type II diabetes mellitus. A 13C nuclear magnetic resonance study. J Clin Invest. 1992;90(4):1323–7. https://doi.org/10.1172/JCI115997. [PMID: 1401068 PMCID: 443176].
37. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults–the evidence report. Obes Res. 1998;6(Suppl 2):51S–209S. [PMID: 9813653].
38. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser. 1995;854:1–452. [PMID: 8594834].
39. Seidell JC, Flegal KM. Assessing obesity: classification and epidemiology. Br Med Bull. 1997;53(2):238–52. [PMID: 9246834].
40. Wang J, Thornton JC, Kolesnik S, Pierson RN Jr. Anthropometry in body composition. An overview. Ann N Y Acad Sci. 2000;904:317–26. [PMID: 10865763].
41. Ferland M, Despres JP, Tremblay A, Pinault S, Nadeau A, Moorjani S, Lupien PJ, Theriault G, Bouchard C. Assessment of adipose tissue distribution by computed axial tomography in obese women: association with body density and anthropometric measurements. Br J Nutr. 1989;61(2):139–48. [PMID: 2706220].
42. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gomez JM, Heitmann BL, Kent-Smith L, Melchior JC, Pirlich M, Scharfetter H, Schols AM, Pichard C. Composition of the EWG. Bioelectrical impedance analysis–part I: review of principles and methods. Clin Nutr. 2004;23(5):1226–43. https://doi.org/10.1016/j.clnu.2004.06.004. [PMID: 15380917].
43. Deurenberg P, Weststrate JA, Seidell JC. Body mass index as a measure of body fatness: age- and sex-specific prediction formulas. Br J Nutr. 1991;65(2):105–14. [PMID: 2043597].
44. Boggs DA, Rosenberg L, Cozier YC, Wise LA, Coogan PF, Ruiz-Narvaez EA, Palmer JR. General and abdominal obesity and risk of death among black women. N Engl J Med. 2011;365(10):901–8. https://doi.org/10.1056/NEJMoa1104119. [PMID: 21899451 PMCID: 3206314].
45. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. BMJ. 1995;311(6998):158–61. [PMID: 7613427 PMCID: 2550221].
46. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr, International Diabetes Federation Task Force on E, Prevention, National Heart L, Blood I, American Heart A, World Heart F, International Atherosclerosis S, International Association for the Study of O. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640–5. https://doi.org/10.1161/CIRCULATIONAHA.109.192644. [PMID: 19805654].
47. Ashwell M, Cole TJ, Dixon AK. Ratio of waist circumference to height is strong predictor of intra-abdominal fat. BMJ. 1996;313(7056):559–60. [PMID: 8790002 PMCID: 2351911].
48. Cox BD, Whichelow M. Ratio of waist circumference to height is better predictor of death than body mass index. BMJ. 1996;313(7070):1487. [PMID: 8973270 PMCID: 2352984].
49. Hsieh SD, Yoshinaga H. Waist/height ratio as a simple and useful predictor of coronary heart disease risk factors in women. Intern Med. 1995;34(12):1147–52. [PMID: 8929639].
50. Vazquez G, Duval S, Jacobs DR Jr, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. Epidemiol Rev. 2007;29:115–28. https://doi.org/10.1093/epirev/mxm008. [PMID: 17494056].
51. Taylor RW, Jones IE, Williams SM, Goulding A. Evaluation of waist circumference, waist-to-hip ratio, and the conicity index as screening tools for high trunk fat mass, as measured by dual-energy X-ray absorptiometry, in children aged 3–19 y. Am J Clin Nutr. 2000;72(2):490–5. [PMID: 10919946].
52. Paniagua JA, Gallego de la Sacristana A, Romero I, Vidal-Puig A, Latre JM, Sanchez E, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. Monounsaturated fat-rich diet prevents central body fat distribution and decreases postprandial adiponectin expression induced by a carbohydrate-rich diet in insulin-resistant subjects. Diabetes Care. 2007;30(7):1717–23. https://doi.org/10.2337/dc06-2220. [PMID: 17384344].
53. Shuster A, Patlas M, Pinthus JH, Mourtzakis M. The clinical importance of visceral adiposity: a critical review of methods for

visceral adipose tissue analysis. Br J Radiol. 2012;85(1009):1–10. https://doi.org/10.1259/bjr/38447238. [PMID: 21937614 PMCID: 3473928].
54. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev. 2000;21(6):697–738. [PMID: 11133069].
55. Hamilton G, Middleton MS, Bydder M, Yokoo T, Schwimmer JB, Kono Y, Patton HM, Lavine JE, Sirlin CB. Effect of PRESS and STEAM sequences on magnetic resonance spectroscopic liver fat quantification. J Magn Reson Imaging JMRI. 2009;30(1):145–52. https://doi.org/10.1002/jmri.21809. [PMID: 19557733 PMCID: 2982807].
56. Kim H, Taksali SE, Dufour S, Befroy D, Goodman TR, Petersen KF, Shulman GI, Caprio S, Constable RT. Comparative MR study of hepatic fat quantification using single-voxel proton spectroscopy, two-point dixon and three-point IDEAL. Magn Reson Med. 2008;59(3):521–7. https://doi.org/10.1002/mrm.21561. [PMID: 18306404 PMCID: 2818363].
57. Stern JH, Rutkowski JM, Scherer PE. Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. Cell Metab. 2016;23(5):770–84. https://doi.org/10.1016/j.cmet.2016.04.011. [PMID: 27166942 PMCID: 4864949].
58. Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, Blomqvist L, Hoffstedt J, Naslund E, Britton T, Concha H, Hassan M, Ryden M, Frisen J, Arner P. Dynamics of fat cell turnover in humans. Nature. 2008;453(7196):783–7. https://doi.org/10.1038/nature06902. [PMID: 18454136].
59. Romere C, Duerrschmid C, Bournat J, Constable P, Jain M, Xia F, Saha PK, Del Solar M, Zhu B, York B, Sarkar P, Rendon DA, Gaber MW, LeMaire SA, Coselli JS, Milewicz DM, Sutton VR, Butte NF, Moore DD, Chopra AR. Asprosin, a fasting-induced glucogenic protein hormone. Cell. 2016;165(3):566–79. https://doi.org/10.1016/j.cell.2016.02.063. [PMID: 27087445 PMCID: 4852710].
60. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJ. Cold-activated brown adipose tissue in healthy men. N Engl J Med. 2009;360(15):1500–8. https://doi.org/10.1056/NEJMoa0808718. [PMID: 19357405].
61. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerback S, Nuutila P. Functional brown adipose tissue in healthy adults. N Engl J Med. 2009;360(15):1518–25. https://doi.org/10.1056/NEJMoa0808949. [PMID: 19357407].
62. Lean ME. Brown adipose tissue in humans. Proc Nutr Soc. 1989;48(2):243–56. [PMID: 2678120].
63. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, Kahn CR. Identification and importance of brown adipose tissue in adult humans. N Engl J Med. 2009;360(15):1509–17. https://doi.org/10.1056/NEJMoa0810780. [PMID: 19357406 PMCID: 2859951].
64. Schulz TJ, Huang P, Huang TL, Xue R, McDougall LE, Townsend KL, Cypess AM, Mishina Y, Gussoni E, Tseng YH. Brown-fat paucity due to impaired BMP signalling induces compensatory browning of white fat. Nature. 2013;495(7441):379–83. https://doi.org/10.1038/nature11943. [PMID: 23485971 PMCID: 3623555].
65. Ouellet V, Routhier-Labadie A, Bellemare W, Lakhal-Chaieb L, Turcotte E, Carpentier AC, Richard D. Outdoor temperature, age, sex, body mass index, and diabetic status determine the prevalence, mass, and glucose-uptake activity of 18F-FDG-detected BAT in humans. J Clin Endocrinol Metab. 2011;96(1):192–9. https://doi.org/10.1210/jc.2010-0989. [PMID: 20943785].
66. Zingaretti MC, Crosta F, Vitali A, Guerrieri M, Frontini A, Cannon B, Nedergaard J, Cinti S. The presence of UCP1 demonstrates that metabolically active adipose tissue in the neck of adult humans truly represents brown adipose tissue. FASEB J. 2009;23(9):3113–20. https://doi.org/10.1096/fj.09-133546. [PMID: 19417078].
67. Cypess AM, Kahn CR. The role and importance of brown adipose tissue in energy homeostasis. Curr Opin Pediatr. 2010;22(4):478–84. https://doi.org/10.1097/MOP.0b013e32833a8d6e. [PMID: 20489634 PMCID: 3593062].
68. Cypess AM, White AP, Vernochet C, Schulz TJ, Xue R, Sass CA, Huang TL, Roberts-Toler C, Weiner LS, Sze C, Chacko AT, Deschamps LN, Herder LM, Truchan N, Glasgow AL, Holman AR, Gavrila A, Hasselgren PO, Mori MA, Molla M, Tseng YH. Anatomical localization, gene expression profiling and functional characterization of adult human neck brown fat. Nat Med. 2013;19(5):635–9. https://doi.org/10.1038/nm.3112. [PMID: 23603815 PMCID: 3650129].
69. Villarroya F, Cereijo R, Villarroya J, Giralt M. Brown adipose tissue as a secretory organ. Nat Rev Endocrinol. 2017;13(1):26–35. https://doi.org/10.1038/nrendo.2016.136. [PMID: 27616452].
70. Cinti S. The adipose organ at a glance. Dis Model Mech. 2012;5(5):588–94. https://doi.org/10.1242/dmm.009662. [PMID: 22915020 PMCID: 3424455].
71. Shan T, Liang X, Bi P, Zhang P, Liu W, Kuang S. Distinct populations of adipogenic and myogenic Myf5-lineage progenitors in white adipose tissues. J Lipid Res. 2013;54(8):2214–24. https://doi.org/10.1194/jlr.M038711. [PMID: 23740968 PMCID: 3708371].
72. Walden TB, Hansen IR, Timmons JA, Cannon B, Nedergaard J. Recruited vs. nonrecruited molecular signatures of brown, "brite," and white adipose tissues. Am J Phys Endocrinol Metab. 2012;302(1):E19–31. https://doi.org/10.1152/ajpendo.00249.2011. [PMID: 21828341].
73. Rosenwald M, Perdikari A, Rulicke T, Wolfrum C. Bi-directional interconversion of brite and white adipocytes. Nat Cell Biol. 2013;15(6):659–67. https://doi.org/10.1038/ncb2740. [PMID: 23624403].
74. Min SY, Kady J, Nam M, Rojas-Rodriguez R, Berkenwald A, Kim JH, Noh HL, Kim JK, Cooper MP, Fitzgibbons T, Brehm MA, Corvera S. Human 'brite/beige' adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice. Nat Med. 2016;22(3):312–8. https://doi.org/10.1038/nm.4031. [PMID: 26808348 PMCID: 4777633].
75. Accili D, Taylor SI. Targeted inactivation of the insulin receptor gene in mouse 3T3-L1 fibroblasts via homologous recombination. Proc Natl Acad Sci U S A. 1991;88(11):4708–12. [PMID: 2052553 PMCID: 51735].
76. Tseng YH, Butte AJ, Kokkotou E, Yechoor VK, Taniguchi CM, Kriauciunas KM, Cypess AM, Niinobe M, Yoshikawa K, Patti ME, Kahn CR. Prediction of preadipocyte differentiation by gene expression reveals role of insulin receptor substrates and necdin. Nat Cell Biol. 2005;7(6):601–11. https://doi.org/10.1038/ncb1259. [PMID: 15895078].
77. Divertie GD, Jensen MD, Miles JM. Stimulation of lipolysis in humans by physiological hypercortisolemia. Diabetes. 1991;40(10):1228–32. [PMID: 1936585].
78. Xu C, He J, Jiang H, Zu L, Zhai W, Pu S, Xu G. Direct effect of glucocorticoids on lipolysis in adipocytes. Mol Endocrinol. 2009;23(8):1161–70. https://doi.org/10.1210/me.2008-0464. [PMID: 19443609].
79. Smas CM, Chen L, Zhao L, Latasa MJ, Sul HS. Transcriptional repression of pref-1 by glucocorticoids promotes 3T3-L1 adipocyte differentiation. J Biol Chem. 1999;274(18):12632–41. [PMID: 10212243].
80. Belanger C, Luu-The V, Dupont P, Tchernof A. Adipose tissue intracrinology: potential importance of local androgen/estrogen

metabolism in the regulation of adiposity. Horm Metab Res = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2002;34(11–12):737–45. https://doi.org/10.1055/s-2002-38265. [PMID: 12660892].
81. Pereira CD, Azevedo I, Monteiro R, Martins MJ. 11beta-Hydroxysteroid dehydrogenase type 1: relevance of its modulation in the pathophysiology of obesity, the metabolic syndrome and type 2 diabetes mellitus. Diabetes Obes Metab. 2012;14(10):869–81. https://doi.org/10.1111/j.1463-1326.2012.01582.x. [PMID: 22321826].
82. Bujalska IJ, Walker EA, Tomlinson JW, Hewison M, Stewart PM. 11Beta-hydroxysteroid dehydrogenase type 1 in differentiating omental human preadipocytes: from de-activation to generation of cortisol. Endocr Res. 2002;28(4):449–61. [PMID: 12530648].
83. Stewart PM, Tomlinson JW. Cortisol, 11 beta-hydroxysteroid dehydrogenase type 1 and central obesity. Trends Endocrinol Metab. 2002;13(3):94–6. [PMID: 11893517].
84. Meseguer A, Puche C, Cabero A. Sex steroid biosynthesis in white adipose tissue. Hormone Metab Res = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2002;34(11–12):731–6. https://doi.org/10.1055/s-2002-38249. [PMID: 12660891].
85. Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Role of thyroid hormone during early brain development. Eur J Endocrinol/Eur Fed Endocr Soc. 2004;151(Suppl 3):U25–37. [PMID: 15554884].
86. Park EA, Song S, Olive M, Roesler WJ. CCAAT-enhancer-binding protein alpha (C/EBP alpha) is required for the thyroid hormone but not the retinoic acid induction of phosphoenolpyruvate carboxykinase (PEPCK) gene transcription. Biochem J. 1997;322(Pt 1):343–9. [PMID: 9078282 PMCID: 1218197].
87. Carmona MC, Iglesias R, Obregon MJ, Darlington GJ, Villarroya F, Giralt M. Mitochondrial biogenesis and thyroid status maturation in brown fat require CCAAT/enhancer-binding protein alpha. J Biol Chem. 2002;277(24):21489–98. https://doi.org/10.1074/jbc.M201710200. [PMID: 11940593].
88. Nam SY, Lobie PE. The mechanism of effect of growth hormone on preadipocyte and adipocyte function. Obes Rev. 2000;1(2):73–86. [PMID: 12119989].
89. Paniagua JA, Escandell-Morales JM, Gil-Contreras D, Berral de la Rosa FJ, Romero-Jimenez M, Gomez-Urbano A, Sanchez-Lopez A, Bellido E, Poyato A, Calatayud B, Vidal-Puig AJ. Central obesity and altered peripheral adipose tissue gene expression characterize the NAFLD patient with insulin resistance: role of nutrition and insulin challenge. Nutrition. 2014;30(2):177–85. https://doi.org/10.1016/j.nut.2013.07.017. [PMID: 24377452].
90. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature. 1998;395(6704):763–70. https://doi.org/10.1038/27376. [PMID: 9796811].
91. Friedman JM. Leptin, leptin receptors, and the control of body weight. Nutr Rev. 1998;56(2 Pt 2):s38–46; discussion s54–75 [PMID: 9564176].
92. Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, Flier JS. Role of leptin in the neuroendocrine response to fasting. Nature. 1996;382(6588):250–2. https://doi.org/10.1038/382250a0. [PMID: 8717038].
93. Chan JL, Heist K, DePaoli AM, Veldhuis JD, Mantzoros CS. The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. J Clin Invest. 2003;111(9):1409–21. https://doi.org/10.1172/JCI17490. [PMID: 12727933 PMCID: 154448].
94. Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, Hughes IA, McCamish MA, O'Rahilly S. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med. 1999;341(12):879–84. https://doi.org/10.1056/NEJM199909163411204. [PMID: 10486419].
95. Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, Karalis A, Mantzoros CS. Recombinant human leptin in women with hypothalamic amenorrhea. N Engl J Med. 2004;351(10):987–97. https://doi.org/10.1056/NEJMoa040388. [PMID: 15342807].
96. Petersen KF, Oral EA, Dufour S, Befroy D, Ariyan C, Yu C, Cline GW, DePaoli AM, Taylor SI, Gorden P, Shulman GI. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. J Clin Invest. 2002;109(10):1345–50. https://doi.org/10.1172/JCI15001. [PMID: 12021250 PMCID: 150981].
97. Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, Wagner AJ, DePaoli AM, Reitman ML, Taylor SI, Gorden P, Garg A. Leptin-replacement therapy for lipodystrophy. N Engl J Med. 2002;346(8):570–8. https://doi.org/10.1056/NEJMoa012437. [PMID: 11856796].
98. Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature. 1998;394(6696):897–901. https://doi.org/10.1038/29795. [PMID: 9732873].
99. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab. 2004;89(6):2548–56. https://doi.org/10.1210/jc.2004-0395. [PMID: 15181022].
100. Unger RH, Zhou YT. Lipotoxicity of beta-cells in obesity and in other causes of fatty acid spillover. Diabetes. 2001;50(Suppl 1):S118–21. [PMID: 11272168].
101. Unger RH, Orci L. Diseases of liporegulation: new perspective on obesity and related disorders. FASEB J. 2001;15(2):312–21. https://doi.org/10.1096/fj.00-0590. [PMID: 11156947].
102. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology. 2004;145(5):2273–82. https://doi.org/10.1210/en.2003-1336. [PMID: 14726444].
103. Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, Murakami K, Ohteki T, Uchida S, Takekawa S, Waki H, Tsuno NH, Shibata Y, Terauchi Y, Froguel P, Tobe K, Koyasu S, Taira K, Kitamura T, Shimizu T, Nagai R, Kadowaki T. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature. 2003;423(6941):762–9. https://doi.org/10.1038/nature01705. [PMID: 12802337].
104. Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, Bihain BE, Lodish HF. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci U S A. 2001;98(4):2005–10. https://doi.org/10.1073/pnas.041591798. [PMID: 11172066 PMCID: 29372].
105. Xu A, Wang Y, Keshaw H, Xu LY, Lam KS, Cooper GJ. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. J Clin Invest. 2003;112(1):91–100. https://doi.org/10.1172/JCI17797. [PMID: 12840063 PMCID: 162288].
106. Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atheroslcerosis. Am J Phys Heart Circ Phys. 2005;288(5):H2031–41. https://doi.org/10.1152/ajpheart.01058.2004. [PMID: 15653761].
107. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006;116(7):1784–92. https://doi.org/10.1172/JCI29126. [PMID: 16823476 PMCID: 1483172].
108. Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC, Matsuzawa Y. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin

sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes. 2001;50(5):1126–33. [PMID: 11334417].
109. Mantzoros CS, Li T, Manson JE, Meigs JB, Hu FB. Circulating adiponectin levels are associated with better glycemic control, more favorable lipid profile, and reduced inflammation in women with type 2 diabetes. J Clin Endocrinol Metab. 2005;90(8):4542–8. https://doi.org/10.1210/jc.2005-0372. [PMID: 15914524].
110. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med. 2006;355(22):2297–307. https://doi.org/10.1056/NEJMoa060326. [PMID: 17135584].
111. Kanhai DA, Kranendonk ME, Uiterwaal CS, van der Graaf Y, Kappelle LJ, Visseren FL. Adiponectin and incident coronary heart disease and stroke. A systematic review and meta-analysis of prospective studies. Obes Rev. 2013;14(7):555–67. https://doi.org/10.1111/obr.12027. [PMID: 23495931].
112. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. Nature. 2001;409(6818):307–12. https://doi.org/10.1038/35053000. [PMID: 11201732].
113. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, Matsuki Y, Murakami M, Ichisaka T, Murakami H, Watanabe E, Takagi T, Akiyoshi M, Ohtsubo T, Kihara S, Yamashita S, Makishima M, Funahashi T, Yamanaka S, Hiramatsu R, Matsuzawa Y, Shimomura I. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science. 2005;307(5708):426–30. https://doi.org/10.1126/science.1097243. [PMID: 15604363].
114. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, Matsuki Y, Murakami M, Ichisaka T, Murakami H, Watanabe E, Takagi T, Akiyoshi M, Ohtsubo T, Kihara S, Yamashita S, Makishima M, Funahashi T, Yamanaka S, Hiramatsu R, Matsuzawa Y, Shimomura I. Retraction. Science. 2007;318(5850):565. https://doi.org/10.1126/science.318.5850.565b. [PMID: 17962537].
115. Arner P. Visfatin–a true or false trail to type 2 diabetes mellitus. J Clin Endocrinol Metab. 2006;91(1):28–30. https://doi.org/10.1210/jc.2005-2391. [PMID: 16401830].
116. de Souza Batista CM, Yang RZ, Lee MJ, Glynn NM, Yu DZ, Pray J, Ndubuizu K, Patil S, Schwartz A, Kligman M, Fried SK, Gong DW, Shuldiner AR, Pollin TI, McLenithan JC. Omentin plasma levels and gene expression are decreased in obesity. Diabetes. 2007;56(6):1655–61. https://doi.org/10.2337/db06-1506. [PMID: 17329619].
117. Tan BK, Adya R, Farhatullah S, Lewandowski KC, O'Hare P, Lehnert H, Randeva HS. Omentin-1, a novel adipokine, is decreased in overweight insulin-resistant women with polycystic ovary syndrome: ex vivo and in vivo regulation of omentin-1 by insulin and glucose. Diabetes. 2008;57(4):801–8. https://doi.org/10.2337/db07-0990. [PMID: 18174521].
118. Tan BK, Adya R, Farhatullah S, Chen J, Lehnert H, Randeva HS. Metformin treatment may increase omentin-1 levels in women with polycystic ovary syndrome. Diabetes. 2010;59(12):3023–31. https://doi.org/10.2337/db10-0124. [PMID: 20852028 PMCID: 2992762].
119. Qi X, Li L, Yang G, Liu J, Li K, Tang Y, Liou H, Boden G. Circulating obestatin levels in normal subjects and in patients with impaired glucose regulation and type 2 diabetes mellitus. Clin Endocrinol. 2007;66(4):593–7. https://doi.org/10.1111/j.1365-2265.2007.02776.x. [PMID: 17371480].
120. Catalan V, Gomez-Ambrosi J, Rotellar F, Silva C, Gil MJ, Rodriguez A, Cienfuegos JA, Salvador J, Fruhbeck G. The obestatin receptor (GPR39) is expressed in human adipose tissue and is down-regulated in obesity-associated type 2 diabetes mellitus. Clin Endocrinol. 2007;66(4):598–601. https://doi.org/10.1111/j.1365-2265.2007.02777.x. [PMID: 17371481].
121. Graham TE, Yang Q, Bluher M, Hammarstedt A, Ciaraldi TP, Henry RR, Wason CJ, Oberbach A, Jansson PA, Smith U, Kahn BB. Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. N Engl J Med. 2006;354(24):2552–63. https://doi.org/10.1056/NEJMoa054862. [PMID: 16775236].
122. Gavi S, Qurashi S, Melendez MM, Mynarcik DC, McNurlan MA, Gelato MC. Plasma retinol-binding protein-4 concentrations are elevated in human subjects with impaired glucose tolerance and type 2 diabetes: response to Cho et al. Diabetes Care. 2007;30(3):e7. https://doi.org/10.2337/dc06-2276; author reply e8 [PMID: 17327302].
123. Gavi S, Stuart LM, Kelly P, Melendez MM, Mynarcik DC, Gelato MC, McNurlan MA. Retinol-binding protein 4 is associated with insulin resistance and body fat distribution in nonobese subjects without type 2 diabetes. J Clin Endocrinol Metab. 2007;92(5):1886–90. https://doi.org/10.1210/jc.2006-1815. [PMID: 17299074].
124. Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci U S A. 1975;72(9):3666–70. [PMID: 1103152 PMCID: 433057].
125. Pennica D, Nedwin GE, Hayflick JS, Seeburg PH, Derynck R, Palladino MA, Kohr WJ, Aggarwal BB, Goeddel DV. Human tumour necrosis factor: precursor structure, expression and homology to lymphotoxin. Nature. 1984;312(5996):724–9. [PMID: 6392892].
126. Locksley RM, Killeen N, Lenardo MJ. The TNF and TNF receptor superfamilies: integrating mammalian biology. Cell. 2001;104(4):487–501. [PMID: 11239407].
127. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259(5091):87–91. [PMID: 7678183].
128. Hotamisligil GS, Johnson RS, Distel RJ, Ellis R, Papaioannou VE, Spiegelman BM. Uncoupling of obesity from insulin resistance through a targeted mutation in aP2, the adipocyte fatty acid binding protein. Science. 1996;274(5291):1377–9. [PMID: 8910278].
129. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature. 1997;389(6651):610–4. https://doi.org/10.1038/39335. [PMID: 9335502].
130. Hofmann C, Lorenz K, Braithwaite SS, Colca JR, Palazuk BJ, Hotamisligil GS, Spiegelman BM. Altered gene expression for tumor necrosis factor-alpha and its receptors during drug and dietary modulation of insulin resistance. Endocrinology. 1994;134(1):264–70. https://doi.org/10.1210/endo.134.1.8275942. [PMID: 8275942].
131. Xing H, Northrop JP, Grove JR, Kilpatrick KE, Su JL, Ringold GM. TNF alpha-mediated inhibition and reversal of adipocyte differentiation is accompanied by suppressed expression of PPARgamma without effects on Pref-1 expression. Endocrinology. 1997;138(7):2776–83. [PMID: 9202217].
132. Ruan H, Hacohen N, Golub TR, Van Parijs L, Lodish HF. Tumor necrosis factor-alpha suppresses adipocyte-specific genes and activates expression of preadipocyte genes in 3T3-L1 adipocytes: nuclear factor-kappaB activation by TNF-alpha is obligatory. Diabetes. 2002;51(5):1319–36. [PMID: 11978627].
133. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest. 2006;116(11):3015–25. https://doi.org/10.1172/JCI28898. [PMID: 17053832 PMCID: 1616196].
134. Bastard JP, Jardel C, Delattre J, Hainque B, Bruckert E, Oberlin F. Evidence for a link between adipose tissue interleukin-6 content

and serum C-reactive protein concentrations in obese subjects. Circulation. 1999;99(16):2221–2. [PMID: 10217702].
135. Fernandez-Real JM, Ricart W. Insulin resistance and chronic cardiovascular inflammatory syndrome. Endocr Rev. 2003;24(3):278–301. [PMID: 12788800].
136. Wang B, Jenkins JR, Trayhurn P. Expression and secretion of inflammation-related adipokines by human adipocytes differentiated in culture: integrated response to TNF-alpha. Am J Phys Endocrinol Metab. 2005;288(4):E731–40. https://doi.org/10.1152/ajpendo.00475.2004. [PMID: 15562246].
137. Chavey C, Lazennec G, Lagarrigue S, Clape C, Iankova I, Teyssier J, Annicotte JS, Schmidt J, Mataki C, Yamamoto H, Sanches R, Guma A, Stich V, Vitkova M, Jardin-Watelet B, Renard E, Strieter R, Tuthill A, Hotamisligil GS, Vidal-Puig A, Zorzano A, Langin D, Fajas L. CXC ligand 5 is an adipose-tissue derived factor that links obesity to insulin resistance. Cell Metab. 2009;9(4):339–49. https://doi.org/10.1016/j.cmet.2009.03.002. [PMID: 19356715 PMCID: 2804846].
138. Duplus E, Glorian M, Forest C. Fatty acid regulation of gene transcription. J Biol Chem. 2000;275(40):30749–52. https://doi.org/10.1074/jbc.R000015200. [PMID: 10934217].
139. Food and Agriculture Organization of the United Nations. Fats and fatty acids in human nutrition: report of an expert consultation: 10–14 November 2008, Geneva. Rome: Food and Agriculture Organization of the United Nations; 2010.
140. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol. 2011;58(20):2047–67. https://doi.org/10.1016/j.jacc.2011.06.063. [PMID: 22051327].
141. Gonzales AM, Orlando RA. Role of adipocyte-derived lipoprotein lipase in adipocyte hypertrophy. Nutr Metab. 2007;4:22. https://doi.org/10.1186/1743-7075-4-22. [PMID: 17971230 PMCID: 2174487].
142. Storch J, Thumser AE. The fatty acid transport function of fatty acid-binding proteins. Biochim Biophys Acta. 2000;1486(1):28–44. [PMID: 10856711].
143. Jakobsson A, Westerberg R, Jacobsson A. Fatty acid elongases in mammals: their regulation and roles in metabolism. Prog Lipid Res. 2006;45(3):237–49. https://doi.org/10.1016/j.plipres.2006.01.004. [PMID: 16564093].
144. Coleman RA, Lee DP. Enzymes of triacylglycerol synthesis and their regulation. Prog Lipid Res. 2004;43(2):134–76. [PMID: 14654091].
145. Yu YH, Zhang Y, Oelkers P, Sturley SL, Rader DJ, Ginsberg HN. Posttranscriptional control of the expression and function of diacylglycerol acyltransferase-1 in mouse adipocytes. J Biol Chem. 2002;277(52):50876–84. https://doi.org/10.1074/jbc.M207353200. [PMID: 12407108].
146. Eckel RH, Kahn SE, Ferrannini E, Goldfine AB, Nathan DM, Schwartz MW, Smith RJ, Smith SR, Endocrine S, American Diabetes A. European Association for the Study of D. Obesity and type 2 diabetes: what can be unified and what needs to be individualized? Diabetes Care. 2011;34(6):1424–30. https://doi.org/10.2337/dc11-0447. [PMID: 21602431 PMCID: 3114323].
147. Sullivan PW, Morrato EH, Ghushchyan V, Wyatt HR, Hill JO. Obesity, inactivity, and the prevalence of diabetes and diabetes-related cardiovascular comorbidities in the U.S., 2000–2002. Diabetes Care. 2005;28(7):1599–603. [PMID: 15983307].
148. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005;365(9467):1333–46. https://doi.org/10.1016/S0140-6736(05)61032-X. [PMID: 15823385].
149. Kahn CR. Banting Lecture. Insulin action, diabetogenes, and the cause of type II diabetes. Diabetes. 1994;43(8):1066–84. [PMID: 8039601].
150. Beck-Nielsen H, Groop LC. Metabolic and genetic characterization of prediabetic states. Sequence of events leading to non-insulin-dependent diabetes mellitus. J Clin Invest. 1994;94(5):1714–21. https://doi.org/10.1172/JCI117518. [PMID: 7962519 PMCID: 294561].
151. Bjorntorp P. Metabolic implications of body fat distribution. Diabetes Care. 1991;14(12):1132–43. [PMID: 1773700].
152. Frontini A, Cinti S. Distribution and development of brown adipocytes in the murine and human adipose organ. Cell Metab. 2010;11(4):253–6. https://doi.org/10.1016/j.cmet.2010.03.004. [PMID: 20374956].
153. Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, Gillman MW, Hennekens CH, Speizer FE, Manson JE. Birthweight and the risk for type 2 diabetes mellitus in adult women. Ann Intern Med. 1999;130(4 Pt 1):278–84. [PMID: 10068385].
154. Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, Barrett-Connor E, Bhargava SK, Birgisdottir BE, Carlsson S, de Rooij SR, Dyck RF, Eriksson JG, Falkner B, Fall C, Forsen T, Grill V, Gudnason V, Hulman S, Hypponen E, Jeffreys M, Lawlor DA, Leon DA, Minami J, Mishra G, Osmond C, Power C, Rich-Edwards JW, Roseboom TJ, Sachdev HS, Syddall H, Thorsdottir I, Vanhala M, Wadsworth M, Yarbrough DE. Birth weight and risk of type 2 diabetes: a systematic review. JAMA. 2008;300(24):2886–97. https://doi.org/10.1001/jama.2008.886. [PMID: 19109117].
155. Dyck RF, Klomp H, Tan L. From "thrifty genotype" to "hefty fetal phenotype": the relationship between high birthweight and diabetes in Saskatchewan Registered Indians. Can J Public Health = Revue canadienne de sante publique. 2001;92(5):340–4. [PMID: 11702485].
156. Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A. Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. Am J Epidemiol. 2007;165(8):849–57. https://doi.org/10.1093/aje/kwk071. [PMID: 17215379].
157. Coleman R, Bell RM. Triacylglycerol synthesis in isolated fat cells. Studies on the microsomal diacylglycerol acyltransferase activity using ethanol-dispersed diacylglycerols. J Biol Chem. 1976;251(15):4537–43. [PMID: 947894].
158. Greenberg AS, Egan JJ, Wek SA, Garty NB, Blanchette-Mackie EJ, Londos C. Perilipin, a major hormonally regulated adipocyte-specific phosphoprotein associated with the periphery of lipid storage droplets. J Biol Chem. 1991;266(17):11341–6. [PMID: 2040638].
159. Bajaj M, Pratipanawatr T, Berria R, Pratipanawatr W, Kashyap S, Cusi K, Mandarino L, DeFronzo RA. Free fatty acids reduce splanchnic and peripheral glucose uptake in patients with type 2 diabetes. Diabetes. 2002;51(10):3043–8. [PMID: 12351445].
160. Kashyap S, Belfort R, Gastaldelli A, Pratipanawatr T, Berria R, Pratipanawatr W, Bajaj M, Mandarino L, DeFronzo R, Cusi K. A sustained increase in plasma free fatty acids impairs insulin secretion in nondiabetic subjects genetically predisposed to develop type 2 diabetes. Diabetes. 2003;52(10):2461–74. [PMID: 14514628].
161. Lupi R, Dotta F, Marselli L, Del Guerra S, Masini M, Santangelo C, Patane G, Boggi U, Piro S, Anello M, Bergamini E, Mosca F, Di Mario U, Del Prato S, Marchetti P. Prolonged exposure to free fatty acids has cytostatic and pro-apoptotic effects on human pancreatic islets: evidence that beta-cell death is caspase mediated, partially dependent on ceramide pathway, and Bcl-2 regulated. Diabetes. 2002;51(5):1437–42. [PMID: 11978640].
162. Rodriguez-Cuenca S, Carobbio S, Velagapudi VR, Barbarroja N, Moreno-Navarrete JM, Tinahones FJ, Fernandez-Real JM, Oresic M, Vidal-Puig A. Peroxisome proliferator-activated receptor gamma-dependent regulation of lipolytic nodes and metabolic flexibility. Mol Cell Biol. 2012;32(8):1555–65. https://

doi.org/10.1128/MCB.06154-11. [PMID: 22310664 PMCID: 3318581]. MCB.06154–11 [pii]].
163. Martin SS, Qasim A, Reilly MP. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. J Am Coll Cardiol. 2008;52(15):1201–10. https://doi.org/10.1016/j.jacc.2008.05.060. [PMID: 18926322 PMCID: 4556270].
164. Kolaczynski JW, Nyce MR, Considine RV, Boden G, Nolan JJ, Henry R, Mudaliar SR, Olefsky J, Caro JF. Acute and chronic effects of insulin on leptin production in humans: Studies in vivo and in vitro. Diabetes. 1996;45(5):699–701. [PMID: 8621027].
165. Asterholm IW, Scherer PE. Enhanced metabolic flexibility associated with elevated adiponectin levels. Am J Pathol. 2010;176(3):1364–76. https://doi.org/10.2353/ajpath.2010.090647. [PMID: 20093494 PMCID: 2832156S0002-9440(10)60448-8 [pii]].
166. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, McCullough AJ, Natale S, Forlani G, Melchionda N. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes. 2001;50(8):1844–50. [PMID: 11473047].
167. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest. 1999;104(6):787–94. https://doi.org/10.1172/JCI7231. [PMID: 10491414 PMCID: 408438].
168. Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev. 2007;87(4):1409–39. https://doi.org/10.1152/physrev.00034.2006. [PMID: 17928588].
169. Nauck MA, Homberger E, Siegel EG, Allen RC, Eaton RP, Ebert R, Creutzfeldt W. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. J Clin Endocrinol Metab. 1986;63(2):492–8. https://doi.org/10.1210/jcem-63-2-492. [PMID: 3522621].
170. Sandoval DA, D'Alessio DA. Physiology of proglucagon peptides: role of glucagon and GLP-1 in health and disease. Physiol Rev. 2015;95(2):513–48. https://doi.org/10.1152/physrev.00013.2014. [PMID: 25834231].
171. DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. Nat Rev Nephrol. 2017;13(1):11–26. https://doi.org/10.1038/nrneph.2016.170. [PMID: 27941935].
172. Obici S, Zhang BB, Karkanias G, Rossetti L. Hypothalamic insulin signaling is required for inhibition of glucose production. Nat Med. 2002;8(12):1376–82. https://doi.org/10.1038/nm798. [PMID: 12426561].
173. Obici S, Feng Z, Karkanias G, Baskin DG, Rossetti L. Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. Nat Neurosci. 2002;5(6):566–72. https://doi.org/10.1038/nn861. [PMID: 12021765].
174. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003;112(12):1821–30. https://doi.org/10.1172/JCI19451. [PMID: 14679177 PMCID: 296998].
175. Curat CA, Miranville A, Sengenes C, Diehl M, Tonus C, Busse R, Bouloumie A. From blood monocytes to adipose tissue-resident macrophages: induction of diapedesis by human mature adipocytes. Diabetes. 2004;53(5):1285–92. [PMID: 15111498].
176. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 2005;115(5):1111–9. https://doi.org/10.1172/JCI25102. [PMID: 15864338 PMCID: 1087185].
177. Fujisaka S, Usui I, Bukhari A, Ikutani M, Oya T, Kanatani Y, Tsuneyama K, Nagai Y, Takatsu K, Urakaze M, Kobayashi M, Tobe K. Regulatory mechanisms for adipose tissue M1 and M2 macrophages in diet-induced obese mice. Diabetes. 2009;58(11):2574–82. https://doi.org/10.2337/db08-1475. [PMID: 19690061 PMCID: 2768159].
178. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest. 2007;117(1):175–84. https://doi.org/10.1172/JCI29881. [PMID: 17200717 PMCID: 1716210].
179. Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med. 2012;18(3):363–74. https://doi.org/10.1038/nm.2627. [PMID: 22395709].
180. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest. 1995;95(5):2409–15. https://doi.org/10.1172/JCI117936. [PMID: 7738205 PMCID: 295872.
181. Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, Lee J, Goldfine AB, Benoist C, Shoelson S, Mathis D. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med. 2009;15(8):930–9. https://doi.org/10.1038/nm.2002. [PMID: 19633656 PMCID: 3115752.
182. Harford KA, Reynolds CM, McGillicuddy FC, Roche HM. Fats, inflammation and insulin resistance: insights to the role of macrophage and T-cell accumulation in adipose tissue. Proc Nutr Soc. 2011;70(4):408–17. https://doi.org/10.1017/S0029665111000565. [PMID: 21835098].
183. Wu D, Molofsky AB, Liang HE, Ricardo-Gonzalez RR, Jouihan HA, Bando JK, Chawla A, Locksley RM. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. Science. 2011;332(6026):243–7. https://doi.org/10.1126/science.1201475. [PMID: 21436399 PMCID: 3144160].
184. Talukdar S, Oh DY, Bandyopadhyay G, Li D, Xu J, McNelis J, Lu M, Li P, Yan Q, Zhu Y, Ofrecio J, Lin M, Brenner MB, Olefsky JM. Neutrophils mediate insulin resistance in mice fed a high-fat diet through secreted elastase. Nat Med. 2012;18(9):1407–12. https://doi.org/10.1038/nm.2885. [PMID: 22863787 PMCID: 3491143].
185. Peraldi P, Hotamisligil GS, Buurman WA, White MF, Spiegelman BM. Tumor necrosis factor (TNF)-alpha inhibits insulin signaling through stimulation of the p55 TNF receptor and activation of sphingomyelinase. J Biol Chem. 1996;271(22):13018–22. [PMID: 8662983].
186. Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M, Shoelson SE. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. Science. 2001;293(5535):1673–7. https://doi.org/10.1126/science.1061620. [PMID: 11533494].
187. Zhang J, Gao Z, Yin J, Quon MJ, Ye J. S6K directly phosphorylates IRS-1 on Ser-270 to promote insulin resistance in response to TNF-(alpha) signaling through IKK2. J Biol Chem. 2008;283(51):35375–82. https://doi.org/10.1074/jbc.M806480200. [PMID: 18952604 PMCID: 2602883].
188. Ye J. Regulation of PPARgamma function by TNF-alpha. Biochem Biophys Res Commun. 2008;374(3):405–8. https://doi.org/10.1016/j.bbrc.2008.07.068]. [PMID: 18655773 PMCID: 2596979].
189. Wen H, Gris D, Lei Y, Jha S, Zhang L, Huang MT, Brickey WJ, Ting JP. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. Nat Immunol. 2011;12(5):408–15. https://doi.org/10.1038/ni.2022. [PMID: 21478880 PMCID: 4090391].
190. Mills KH, Dunne A. Immune modulation: IL-1, master mediator or initiator of inflammation. Nat Med. 2009;15(12):1363–4. https://doi.org/10.1038/nm1209-1363. [PMID: 19966773].

191. Netea MG, Nold-Petry CA, Nold MF, Joosten LA, Opitz B, van der Meer JH, van de Veerdonk FL, Ferwerda G, Heinhuis B, Devesa I, Funk CJ, Mason RJ, Kullberg BJ, Rubartelli A, van der Meer JW, Dinarello CA. Differential requirement for the activation of the inflammasome for processing and release of IL-1beta in monocytes and macrophages. Blood. 2009;113(10):2324–35. https://doi.org/10.1182/blood-2008-03-146720. [PMID: 19104081 PMCID: 2652374].
192. Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, Ravussin E, Stephens JM, Dixit VD. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med. 2011;17(2):179–88. https://doi.org/10.1038/nm.2279. [PMID: 21217695 PMCID: 3076025].
193. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112(12):1796–808. https://doi.org/10.1172/JCI19246. [PMID: 14679176 PMCID: 296995].
194. Wieckowska A, Papouchado BG, Li Z, Lopez R, Zein NN, Feldstein AE. Increased hepatic and circulating interleukin-6 levels in human nonalcoholic steatohepatitis. Am J Gastroenterol. 2008;103(6):1372–9. https://doi.org/10.1111/j.1572--0241.2007.01774.x. [PMID: 18510618].
195. Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE. Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. Obes Res. 2001;9(7):414–7. https://doi.org/10.1038/oby.2001.54. [PMID: 11445664].
196. Ruge T, Lockton JA, Renstrom F, Lystig T, Sukonina V, Svensson MK, Eriksson JW. Acute hyperinsulinemia raises plasma interleukin-6 in both nondiabetic and type 2 diabetes mellitus subjects, and this effect is inversely associated with body mass index. Metab Clin Exp. 2009;58(6):860–6. https://doi.org/10.1016/j.metabol.2009.02.010. [PMID: 19375766].
197. Ellingsgaard H, Hauselmann I, Schuler B, Habib AM, Baggio LL, Meier DT, Eppler E, Bouzakri K, Wueest S, Muller YD, Hansen AM, Reinecke M, Konrad D, Gassmann M, Reimann F, Halban PA, Gromada J, Drucker DJ, Gribble FM, Ehses JA, Donath MY. Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. Nat Med. 2011;17(11):1481–9. https://doi.org/10.1038/nm.2513. [PMID: 22037645 PMCID: 4286294].
198. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol. 2012;8(8):457–65. https://doi.org/10.1038/nrendo.2012.49. [PMID: 22473333].
199. Pedersen BK. A muscular twist on the fate of fat. N Engl J Med. 2012;366(16):1544–5. https://doi.org/10.1056/NEJMcibr1201024. [PMID: 22512488].
200. van Exel E, Gussekloo J, de Craen AJ, Frolich M, Bootsma-Van Der Wiel A, Westendorp RG, Leiden 85 Plus S. Low production capacity of interleukin-10 associates with the metabolic syndrome and type 2 diabetes: the Leiden 85-Plus Study. Diabetes. 2002;51(4):1088–92. [PMID: 11916930].
201. Cancello R, Henegar C, Viguerie N, Taleb S, Poitou C, Rouault C, Coupaye M, Pelloux V, Hugol D, Bouillot JL, Bouloumie A, Barbatelli G, Cinti S, Svensson PA, Barsh GS, Zucker JD, Basdevant A, Langin D, Clement K. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. Diabetes. 2005;54(8):2277–86. [PMID: 16046292].
202. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. Science. 2005;307(5708):384–7. https://doi.org/10.1126/science.1104343. [PMID: 15662004].
203. Stump CS, Short KR, Bigelow ML, Schimke JM, Nair KS. Effect of insulin on human skeletal muscle mitochondrial ATP production, protein synthesis, and mRNA transcripts. Proc Natl Acad Sci U S A. 2003;100(13):7996–8001. https://doi.org/10.1073/pnas.1332551100. [PMID: 12808136 PMCID: 164701].
204. Asmann YW, Stump CS, Short KR, Coenen-Schimke JM, Guo Z, Bigelow ML, Nair KS. Skeletal muscle mitochondrial functions, mitochondrial DNA copy numbers, and gene transcript profiles in type 2 diabetic and nondiabetic subjects at equal levels of low or high insulin and euglycemia. Diabetes. 2006;55(12):3309–19. https://doi.org/10.2337/db05-1230. [PMID: 17130474].
205. Kelley DE, He J, Menshikova EV, Ritov VB. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. Diabetes. 2002;51(10):2944–50. [PMID: 12351431].
206. Kelley DE, Goodpaster B, Wing RR, Simoneau JA. Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. Am J Physiol. 1999;277(6 Pt 1):E1130–41. [PMID: 10600804].
207. Simoneau JA, Veerkamp JH, Turcotte LP, Kelley DE. Markers of capacity to utilize fatty acids in human skeletal muscle: relation to insulin resistance and obesity and effects of weight loss. FASEB J. 1999;13(14):2051–60. [PMID: 10544188].
208. Szendroedi J, Phielix E, Roden M. The role of mitochondria in insulin resistance and type 2 diabetes mellitus. Nat Rev Endocrinol. 2011;8(2):92–103. https://doi.org/10.1038/nrendo.2011.138. [PMID: 21912398].
209. Hwang H, Bowen BP, Lefort N, Flynn CR, De Filippis EA, Roberts C, Smoke CC, Meyer C, Hojlund K, Yi Z, Mandarino LJ. Proteomics analysis of human skeletal muscle reveals novel abnormalities in obesity and type 2 diabetes. Diabetes. 2010;59(1):33–42. https://doi.org/10.2337/db09-0214. [PMID: 19833877 PMCID: 2797941].
210. Turner N, Heilbronn LK. Is mitochondrial dysfunction a cause of insulin resistance? Trends Endocrinol Metab. 2008;19(9):324–30. https://doi.org/10.1016/j.tem.2008.08.001. [PMID: 18804383].
211. Turner N, Bruce CR, Beale SM, Hoehn KL, So T, Rolph MS, Cooney GJ. Excess lipid availability increases mitochondrial fatty acid oxidative capacity in muscle: evidence against a role for reduced fatty acid oxidation in lipid-induced insulin resistance in rodents. Diabetes. 2007;56(8):2085–92. https://doi.org/10.2337/db07-0093. [PMID: 17519422].
212. Hancock CR, Han DH, Chen M, Terada S, Yasuda T, Wright DC, Holloszy JO. High-fat diets cause insulin resistance despite an increase in muscle mitochondria. Proc Natl Acad Sci U S A. 2008;105(22):7815–20. https://doi.org/10.1073/pnas.0802057105. [PMID: 18509063 PMCID: 2409421].
213. Turner N, Hariharan K, TidAng J, Frangioudakis G, Beale SM, Wright LE, Zeng XY, Leslie SJ, Li JY, Kraegen EW, Cooney GJ, Ye JM. Enhancement of muscle mitochondrial oxidative capacity and alterations in insulin action are lipid species dependent: potent tissue-specific effects of medium-chain fatty acids. Diabetes. 2009;58(11):2547–54. https://doi.org/10.2337/db09-0784. [PMID: 19720794 PMCID: 2768163].
214. Pagel-Langenickel I, Bao J, Pang L, Sack MN. The role of mitochondria in the pathophysiology of skeletal muscle insulin resistance. Endocr Rev. 2010;31(1):25–51 [. [PMID: 19861693 PMCID: 2852205]. https://doi.org/10.1210/er.2009-0003].
215. Muoio DM. Intramuscular triacylglycerol and insulin resistance: guilty as charged or wrongly accused? Biochim Biophys Acta. 2010;1801(3):281–8. https://doi.org/10.1016/j.bbalip.2009.11.007. [PMID: 19958841 PMCID: 4428562].
216. Brunmair B, Staniek K, Gras F, Scharf N, Althaym A, Clara R, Roden M, Gnaiger E, Nohl H, Waldhausl W, Furnsinn C. Thiazolidinediones, like metformin, inhibit respiratory complex I: a common mechanism contributing to their antidiabetic actions? Diabetes. 2004;53(4):1052–9. [PMID: 15047621].
217. Roden M, Price TB, Perseghin G, Petersen KF, Rothman DL, Cline GW, Shulman GI. Mechanism of free fatty acid-induced insulin resistance in humans. J Clin Invest. 1996;97(12):2859–65.

https://doi.org/10.1172/JCI118742. [PMID: 8675698 PMCID: 507380].
218. Samocha-Bonet D, Campbell LV, Mori TA, Croft KD, Greenfield JR, Turner N, Heilbronn LK. Overfeeding reduces insulin sensitivity and increases oxidative stress, without altering markers of mitochondrial content and function in humans. PLoS One. 2012;7(5):e36320. https://doi.org/10.1371/journal.pone.0036320. [PMID: 22586466 PMCID: 3346759].
219. Boushel R, Gnaiger E, Schjerling P, Skovbro M, Kraunsoe R, Dela F. Patients with type 2 diabetes have normal mitochondrial function in skeletal muscle. Diabetologia. 2007;50(4):790–6. https://doi.org/10.1007/s00125-007-0594-3. [PMID: 17334651 PMCID: 1820754].
220. Paolisso G, Gambardella A, Tagliamonte MR, Saccomanno F, Salvatore T, Gualdiero P, D'Onofrio MV, Howard BV. Does free fatty acid infusion impair insulin action also through an increase in oxidative stress? J Clin Endocrinol Metab. 1996;81(12):4244–8. https://doi.org/10.1210/jcem.81.12.8954022. [PMID: 8954022].
221. De Mattia G, Bravi MC, Laurenti O, Cassone-Faldetta M, Armiento A, Ferri C, Balsano F. Influence of reduced glutathione infusion on glucose metabolism in patients with non-insulin-dependent diabetes mellitus. Metab Clin Exp. 1998;47(8):993–7. [PMID: 9711998].
222. Mielgo-Ayuso J, Barrenechea L, Alcorta P, Larrarte E, Margareto J, Labayen I. Effects of dietary supplementation with epigallocatechin-3-gallate on weight loss, energy homeostasis, cardiometabolic risk factors and liver function in obese women: randomised, double-blind, placebo-controlled clinical trial. Br J Nutr. 2014;111(7):1263–71. https://doi.org/10.1017/S0007114513003784. [PMID: 24299662].
223. Czernichow S, Vergnaud AC, Galan P, Arnaud J, Favier A, Faure H, Huxley R, Hercberg S, Ahluwalia N. Effects of long-term antioxidant supplementation and association of serum antioxidant concentrations with risk of metabolic syndrome in adults. Am J Clin Nutr. 2009;90(2):329–35. https://doi.org/10.3945/ajcn.2009.27635. [PMID: 19491388].
224. Schroder M, Kaufman RJ. ER stress and the unfolded protein response. Mutat Res. 2005;569(1–2):29–63. https://doi.org/10.1016/j.mrfmmm.2004.06.056. [PMID: 15603751].
225. Ozcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, Ozdelen E, Tuncman G, Gorgun C, Glimcher LH, Hotamisligil GS. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science. 2004;306(5695):457–61. https://doi.org/10.1126/science.1103160. [PMID: 15486293].
226. de Luca C, Olefsky JM. Stressed out about obesity and insulin resistance. Nat Med. 2006;12(1):41–2. https://doi.org/10.1038/nm0106-41; discussion 42 [PMID: 16397561].
227. Ozcan L, Ergin AS, Lu A, Chung J, Sarkar S, Nie D, Myers MG Jr, Ozcan U. Endoplasmic reticulum stress plays a central role in development of leptin resistance. Cell Metab. 2009;9(1):35–51. https://doi.org/10.1016/j.cmet.2008.12.004. [PMID: 19117545].
228. Kars M, Yang L, Gregor MF, Mohammed BS, Pietka TA, Finck BN, Patterson BW, Horton JD, Mittendorfer B, Hotamisligil GS, Klein S. Tauroursodeoxycholic Acid may improve liver and muscle but not adipose tissue insulin sensitivity in obese men and women. Diabetes. 2010;59(8):1899–905. https://doi.org/10.2337/db10-0308. [PMID: 20522594 PMCID: 2911053].
229. Muoio DM, Dohm GL, Fiedorek FT Jr, Tapscott EB, Coleman RA. Leptin directly alters lipid partitioning in skeletal muscle. Diabetes. 1997;46(8):1360–3. [PMID: 9231663].
230. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest. 2005;115(5):1343–51. https://doi.org/10.1172/JCI23621. [PMID: 15864352 PMCID: 1087172.
231. Paniagua JA. Nutrition, insulin resistance and dysfunctional adipose tissue determine the different components of metabolic syndrome. World J Diabetes. 2016;7(19):483–514. https://doi.org/10.4239/wjd.v7.i19.483. [PMID: 27895819 PMCID: 5107710].
232. Utzschneider KM, Kahn SE. Review: The role of insulin resistance in nonalcoholic fatty liver disease. J Clin Endocrinol Metab. 2006;91(12):4753–61. https://doi.org/10.1210/jc.2006-0587. [PMID: 16968800].
233. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, Tio F, Hardies J, Darland C, Musi N, Webb A, Portillo-Sanchez P. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med. 2016;165(5):305–15. https://doi.org/10.7326/M15-1774. [PMID: 27322798].
234. Kugelmas M, Hill DB, Vivian B, Marsano L, McClain CJ. Cytokines and NASH: a pilot study of the effects of lifestyle modification and vitamin E. Hepatology. 2003;38(2):413–9. https://doi.org/10.1053/jhep.2003.50316. [PMID: 12883485].
235. Steil GM, Trivedi N, Jonas JC, Hasenkamp WM, Sharma A, Bonner-Weir S, Weir GC. Adaptation of beta-cell mass to substrate oversupply: enhanced function with normal gene expression. Am J Phys Endocrinol Metab. 2001;280(5):E788–96. [PMID: 11287362].
236. Chen C, Hosokawa H, Bumbalo LM, Leahy JL. Mechanism of compensatory hyperinsulinemia in normoglycemic insulin-resistant spontaneously hypertensive rats. Augmented enzymatic activity of glucokinase in beta-cells. J Clin Invest. 1994;94(1):399–404. https://doi.org/10.1172/JCI117335. [PMID: 8040280 PMCID: 296322].
237. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes. 2003;52(1):102–10. [PMID: 12502499].
238. Prentki M. New insights into pancreatic beta-cell metabolic signaling in insulin secretion. Eur J Endocrinol/Eur Fed Endocr Soc. 1996;134(3):272–86. [PMID: 8616523].
239. Lebrun P, Montminy MR, Van Obberghen E. Regulation of the pancreatic duodenal homeobox-1 protein by DNA-dependent protein kinase. J Biol Chem. 2005;280(46):38203–10. https://doi.org/10.1074/jbc.M504842200. [PMID: 16166097].
240. Roduit R, Nolan C, Alarcon C, Moore P, Barbeau A, Delghingaro-Augusto V, Przybykowski E, Morin J, Masse F, Massie B, Ruderman N, Rhodes C, Poitout V, Prentki M. A role for the malonyl-CoA/long-chain acyl-CoA pathway of lipid signaling in the regulation of insulin secretion in response to both fuel and nonfuel stimuli. Diabetes. 2004;53(4):1007–19. [PMID: 15047616].
241. Prentki M, Joly E, El-Assaad W, Roduit R. Malonyl-CoA signaling, lipid partitioning, and glucolipotoxicity: role in beta-cell adaptation and failure in the etiology of diabetes. Diabetes. 2002;51(Suppl 3):S405–13. [PMID: 12475783].
242. Paniagua JA, de la Sacristana AG, Sanchez E, Romero I, Vidal-Puig A, Berral FJ, Escribano A, Moyano MJ, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. A MUFA-rich diet improves posprandial glucose, lipid and GLP-1 responses in insulin-resistant subjects. J Am Coll Nutr. 2007;26(5):434–44. [PMID: 17914131].
243. Nolan CJ, Leahy JL, Delghingaro-Augusto V, Moibi J, Soni K, Peyot ML, Fortier M, Guay C, Lamontagne J, Barbeau A, Przybytkowski E, Joly E, Masiello P, Wang S, Mitchell GA, Prentki M. Beta cell compensation for insulin resistance in Zucker fatty rats: increased lipolysis and fatty acid signalling. Diabetologia. 2006;49(9):2120–30. https://doi.org/10.1007/s00125-006-0305-5. [PMID: 16868750].

244. Yusta B, Baggio LL, Estall JL, Koehler JA, Holland DP, Li H, Pipeleers D, Ling Z, Drucker DJ. GLP-1 receptor activation improves beta cell function and survival following induction of endoplasmic reticulum stress. Cell Metab. 2006;4(5):391–406. https://doi.org/10.1016/j.cmet.2006.10.001. [PMID: 17084712].
245. Drucker DJ. The biology of incretin hormones. Cell Metab. 2006;3(3):153–65. https://doi.org/10.1016/j.cmet.2006.01.004. [PMID: 16517403].
246. Muscelli E, Mari A, Casolaro A, Camastra S, Seghieri G, Gastaldelli A, Holst JJ, Ferrannini E. Separate impact of obesity and glucose tolerance on the incretin effect in normal subjects and type 2 diabetic patients. Diabetes. 2008;57(5):1340–8. https://doi.org/10.2337/db07-1315. [PMID: 18162504].
247. Ahren B. Autonomic regulation of islet hormone secretion--implications for health and disease. Diabetologia. 2000;43(4):393–410. https://doi.org/10.1007/s001250051322. [PMID: 10819232].
248. Yoon KH, Ko SH, Cho JH, Lee JM, Ahn YB, Song KH, Yoo SJ, Kang MI, Cha BY, Lee KW, Son HY, Kang SK, Kim HS, Lee IK, Bonner-Weir S. Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea. J Clin Endocrinol Metab. 2003;88(5):2300–8. https://doi.org/10.1210/jc.2002-020735. [PMID: 12727989].
249. Robertson RP. Chronic oxidative stress as a central mechanism for glucose toxicity in pancreatic islet beta cells in diabetes. J Biol Chem. 2004;279(41):42351–4. https://doi.org/10.1074/jbc.R400019200. [PMID: 15258147].
250. Donath MY, Ehses JA, Maedler K, Schumann DM, Ellingsgaard H, Eppler E, Reinecke M. Mechanisms of beta-cell death in type 2 diabetes. Diabetes. 2005;54(Suppl 2):S108–13. [PMID: 16306327].
251. Brownlee M. A radical explanation for glucose-induced beta cell dysfunction. J Clin Invest. 2003;112(12):1788–90. https://doi.org/10.1172/JCI20501. [PMID: 14679173 PMCID: 297003].
252. Krauss S, Zhang CY, Scorrano L, Dalgaard LT, St-Pierre J, Grey ST, Lowell BB. Superoxide-mediated activation of uncoupling protein 2 causes pancreatic beta cell dysfunction. J Clin Invest. 2003;112(12):1831–42. https://doi.org/10.1172/JCI19774. [PMID: 14679178 PMCID: 297000].
253. Oyadomari S, Araki E, Mori M. Endoplasmic reticulum stress-mediated apoptosis in pancreatic beta-cells. Apoptosis. 2002;7(4):335–45. [PMID: 12101393].
254. Puri S, Folias AE, Hebrok M. Plasticity and dedifferentiation within the pancreas: development, homeostasis, and disease. Cell Stem Cell. 2015;16(1):18–31. https://doi.org/10.1016/j.stem.2014.11.001. [PMID: 25465113 PMCID: 4289422].
255. Hosoya M, Kunisada Y, Kurisaki A, Asashima M. Induction of differentiation of undifferentiated cells into pancreatic beta cells in vertebrates. Int J Dev Biol. 2012;56(5):313–23. https://doi.org/10.1387/ijdb.123522mh. [PMID: 22689376].
256. Kim JB, Sarraf P, Wright M, Yao KM, Mueller E, Solanes G, Lowell BB, Spiegelman BM. Nutritional and insulin regulation of fatty acid synthetase and leptin gene expression through ADD1/SREBP1. J Clin Invest. 1998;101(1):1–9. https://doi.org/10.1172/JCI1411. [PMID: 9421459 PMCID: 508533].
257. Kim JB, Wright HM, Wright M, Spiegelman BM. ADD1/SREBP1 activates PPARgamma through the production of endogenous ligand. Proc Natl Acad Sci U S A. 1998;95(8):4333–7. [PMID: 9539737 PMCID: 22489].
258. Spiegelman BM, Frank M, Green H. Molecular cloning of mRNA from 3T3 adipocytes. Regulation of mRNA content for glycerophosphate dehydrogenase and other differentiation-dependent proteins during adipocyte development. J Biol Chem. 1983;258(16):10083–9. [PMID: 6411703].
259. Mandrup S, Lane MD. Regulating adipogenesis. J Biol Chem. 1997;272(9):5367–70. [PMID: 9102400].
260. Sung HK, Doh KO, Son JE, Park JG, Bae Y, Choi S, Nelson SM, Cowling R, Nagy K, Michael IP, Koh GY, Adamson SL, Pawson T, Nagy A. Adipose vascular endothelial growth factor regulates metabolic homeostasis through angiogenesis. Cell Metab. 2013;17(1):61–72. https://doi.org/10.1016/j.cmet.2012.12.010. [PMID: 23312284]. S1550-4131(12)00501-3 [pii]].
261. Maroto M, Bone RA, Dale JK. Somitogenesis. Development. 2012;139(14):2453–6. https://doi.org/10.1242/dev.069310. [PMID: 22736241].
262. Seale P, Bjork B, Yang W, Kajimura S, Chin S, Kuang S, Scime A, Devarakonda S, Conroe HM, Erdjument-Bromage H, Tempst P, Rudnicki MA, Beier DR, Spiegelman BM. PRDM16 controls a brown fat/skeletal muscle switch. Nature. 2008;454(7207):961–7. https://doi.org/10.1038/nature07182. [PMID: 18719582 PMCID: 2583329].
263. Kajimura S, Seale P, Tomaru T, Erdjument-Bromage H, Cooper MP, Ruas JL, Chin S, Tempst P, Lazar MA, Spiegelman BM. Regulation of the brown and white fat gene programs through a PRDM16/CtBP transcriptional complex. Genes Dev. 2008;22(10):1397–409. https://doi.org/10.1101/gad.1666108. [PMID: 18483224 PMCID: 2377193].
264. Tseng YH, Kokkotou E, Schulz TJ, Huang TL, Winnay JN, Taniguchi CM, Tran TT, Suzuki R, Espinoza DO, Yamamoto Y, Ahrens MJ, Dudley AT, Norris AW, Kulkarni RN, Kahn CR. New role of bone morphogenetic protein 7 in brown adipogenesis and energy expenditure. Nature. 2008;454(7207):1000–4. https://doi.org/10.1038/nature07221. [PMID: 18719589 PMCID: 2745972].
265. Bullo M, Garcia-Lorda P, Megias I, Salas-Salvado J. Systemic inflammation, adipose tissue tumor necrosis factor, and leptin expression. Obes Res. 2003;11(4):525–31. https://doi.org/10.1038/oby.2003.74. [PMID: 12690081].
266. Prieur X, Mok CY, Velagapudi VR, Nunez V, Fuentes L, Montaner D, Ishikawa K, Camacho A, Barbarroja N, O'Rahilly S, Sethi JK, Dopazo J, Oresic M, Ricote M, Vidal-Puig A. Differential lipid partitioning between adipocytes and tissue macrophages modulates macrophage lipotoxicity and M2/M1 polarization in obese mice. Diabetes. 2011;60(3):797–809. https://doi.org/10.2337/db10-0705. [PMID: 21266330 PMCID: 3046840].
267. Rosen BS, Cook KS, Yaglom J, Groves DL, Volanakis JE, Damm D, White T, Spiegelman BM. Adipsin and complement factor D activity: an immune-related defect in obesity. Science. 1989;244(4911):1483–7. [PMID: 2734615].
268. Kasbi Chadli F, Andre A, Prieur X, Loirand G, Meynier A, Krempf M, Nguyen P, Ouguerram K. n-3 PUFA prevent metabolic disturbances associated with obesity and improve endothelial function in golden Syrian hamsters fed with a high-fat diet. Br J Nutr. 2012;107(9):1305–15. https://doi.org/10.1017/S0007114511004387. [PMID: 21920060].
269. Guilherme A, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol. 2008;9(5):367–77. https://doi.org/10.1038/nrm2391. [PMID: 18401346 PMCID: 2886982].
270. Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. J Clin Invest. 2011;121(6):2094–101. https://doi.org/10.1172/JCI45887. [PMID: 21633177 PMCID: 3104761].
271. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412–9. [PMID: 3899825].
272. Hotamisligil GS. Inflammation, TNF alpha and insulin resistance. Philadelphia: Lippincott-Raven Publishers; 2003.
273. Hirosumi J, Tuncman G, Chang L, Gorgun CZ, Uysal KT, Maeda K, Karin M, Hotamisligil GS. A central role for JNK in obesity and insulin resistance. Nature. 2002;420(6913):333–6. https://doi.org/10.1038/nature01137. [PMID: 12447443].

274. Despres JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, Rodes-Cabau J, Bertrand OF, Poirier P. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol. 2008;28(6):1039–49. https://doi.org/10.1161/ATVBAHA.107.159228. [PMID: 18356555].
275. Kim JY, van de Wall E, Laplante M, Azzara A, Trujillo ME, Hofmann SM, Schraw T, Durand JL, Li H, Li G, Jelicks LA, Mehler MF, Hui DY, Deshaies Y, Shulman GI, Schwartz GJ, Scherer PE. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest. 2007;117(9):2621–37. https://doi.org/10.1172/JCI31021. [PMID: 17717599 PMCID: 1950456].
276. Meier JJ, Bonadonna RC. Role of reduced beta-cell mass versus impaired beta-cell function in the pathogenesis of type 2 diabetes. Diabetes Care. 2013;36(Suppl 2):S113–9. https://doi.org/10.2337/dcS13-2008. [PMID: 23882035 PMCID: 3920783].
277. Garber AJ. Incretin effects on beta-cell function, replication, and mass: the human perspective. Diabetes Care. 2011;34(Suppl 2):S258–63. https://doi.org/10.2337/dc11-s230. [PMID: 21525465 PMCID: 3632189].