

METABOLIC SYNDROME

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ABSTRACT

Significant interest exists in understanding the shared metabolic dysregulation leading to obesity, diabetes, and cardiovascular disease (CVD). Hence came the concept of the “metabolic syndrome” (MetS). Reaven first described MetS in his 1988 Banting lecture as “Syndrome X”. Reaven suggested that the syndrome hinged on the existence of insulin resistance and resulted in glucose intolerance, hypertension and dyslipidemia. The World Health Organization (WHO) produced the first formalized definition of the MetS in 1998. Since then multiple definitions of the syndrome have been proposed, the most recent being the Harmonized Definition where 3 of the 5 risk factors are present: enlarged waist circumference with population-specific and country-specific criteria; triglycerides ≥ 150 mg/dL, HDL-C < 40 mg/dL in men and < 50 mg/dL in women, systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg and fasting glucose > 100 mg/dL, with the inclusion of patients taking medication to manage hypertriglyceridemia, low HDL-C, hypertension, and hyperglycemia. The National Health and Nutrition Examination Survey (NHANES) estimated the overall prevalence of MetS in adults (aged ≥ 20 years) in the United States as 33% from 2003 to 2012. The high prevalence is particularly alarming given that MetS also predisposes to a number of serious conditions beyond diabetes and CVD including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), polycystic ovarian syndrome (PCOS), obstructive sleep apnea (OSA), cancer, and many other serious disease states. Hence, early identification and intervention are warranted. Lifestyle modification is the foundational intervention in treatment of MetS. Specifically, a healthy low-calorie, low fat diet and moderate physical activity of at least 150 minutes/week, resulting in a weight reduction of 7%. Obesity, hypertension and dyslipidemia may also be treated pharmacologically to meet individualized patient goals. Beyond the clinic imperative around MetS are its pathophysiologic underpinnings. This review will focus on the investigative work into the proximal origins of the MetS. Defects in insulin signaling occur in a shared environment of pro-inflammation, untoward adipokines coming from dysregulated fatty acid metabolism, as well as novel pathways involving the gut microbiota. Collectively, MetS continues to exist as a fertile area of research yielding significant insights into early events leading to the most prevalent cause of human morbidity and mortality. For in depth review of all related aspects of endocrinology, visit www.endotext.org.

HISTORY AND DEFINITIONS

The metabolic syndrome (MetS) is a compilation of risk factors that predispose individuals to the development of type 2 diabetes (T2DM) and cardiovascular disease (CVD). Reaven (1) first described MetS in his 1988 Banting lecture as "Syndrome X." Reaven suggested that insulin resistance clustered together with glucose intolerance, dyslipidemia, and hypertension to increase the risk of CVD. The initial definition of metabolic syndrome included impaired glucose tolerance (IGT), hyperinsulinemia, elevated triglycerides (TG), and reduced high-density lipoprotein cholesterol (HDL-C). Hyperuricemia, microvascular angina, and elevated plasminogen activator inhibitor 1 (PAI-1) were later proposed as possible additional components of the same syndrome (1,2). Obesity was not included as part of Syndrome X as Reaven believed that insulin resistance, not obesity, was the common denominator. Reaven noted that all of the elements of Syndrome X could occur in non-obese individuals, and while he acknowledged that obesity could lead to a decrease in insulin mediated glucose uptake, he stressed that obesity was only one of the environmental factors that affect insulin sensitivity (3,4).

The World Health Organization (WHO) produced the first formalized definition of the MetS in 1998. The working definition included impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or diabetes mellitus and/or insulin resistance (as measured using a hyperinsulinemic euglycemic clamp study) together with two or more additional components. Additional components included hypertension (defined as a blood pressure $\geq 160/90$ mm Hg), raised plasma triglycerides (≥ 150 mg/dl) and/or low HDL-C (< 35 mg/dl for men and < 39 mg/dl for women), central obesity (defined either as body mass index (BMI) > 30 kg/m² or waist to hip ratio > 0.90 for males and > 0.85 for females) and microalbuminuria (5). Critics questioned the practicality of this definition given the need for a hyperinsulinemic clamp study. Others argued that measuring waist circumference was superior in terms of convenience to the waist to hip ratio with similar correlations to obesity. Additionally, there was a question about the value of including microalbuminuria in the definition as there was insufficient evidence of a connection with insulin resistance (5).

These critiques led to the first revision of the definition of the syndrome in 1999 by the European Group for the Study of Insulin Resistance (EGIR). They renamed the syndrome the "insulin resistance syndrome" (IRS) as it included non-metabolic features. They excluded patients with diabetes because of the difficulty of measuring insulin resistance in these individuals. The need for hyperinsulinemic clamp studies was obviated by defining insulin resistance as a fasting insulin level above the 75th percentile for the population. Additional criteria (elements associated with increased risk of coronary artery disease by the Second Joint Task Force of European and other Societies on Coronary Prevention) were also included, namely obesity (defined as waist circumference ≥ 94 cm (37 inches) for men and ≥ 80 cm (32 inches) for women), hypertension (now defined as a blood pressure $\geq 140/90$ mm Hg) and dyslipidemia (with triglycerides ≥ 180 mg/dl or HDL-C ≤ 39). Additionally, microalbuminuria was omitted from the definition (6).

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) recognized that these multiple metabolic elements were cardiovascular risk factors and renamed the constellation of these metabolic risk factors as "The Metabolic Syndrome" (7). The criteria included any three of the following: obesity (defined as waist circumference ≥ 102 cm (40 inches) in males and ≥ 88 cm (35 inches) in females (based on the 1998 National Institutes of Health (NIH) obesity clinical guidelines; pediatric definitions use standardized Z-scores rather than waist circumference (8)), hypertension (defined as blood pressure $\geq 130/85$ mm Hg based on the Joint National Committee guidelines), fasting glucose > 110 mg/dL, triglycerides ≥ 150 mg/dL and HDL-C < 40 mg/dL. Additionally, in this report MetS

was recognized as a secondary target of risk reduction therapy after the primary target of LDL cholesterol (7).

In 2003, the American Association of Clinical Endocrinologists (AACE) modified the ATP III criteria and restored the condition to the name “Insulin Resistance Syndrome,” again highlighting the central role of insulin resistance in the pathogenesis of the syndrome (9). This definition did not rely on strict diagnostic criteria. The components of the syndrome included some degree of glucose intolerance (but not overt diabetes), abnormal uric acid metabolism, dyslipidemia, hemodynamic changes (including hypertension), prothrombotic factors, markers of inflammation, and endothelial dysfunction. The AACE position statement also identified factors that increased the likelihood of developing the insulin resistance syndrome, including a diagnosis of CVD, hypertension, polycystic ovarian syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD) or acanthosis nigricans, a family history of T2DM, hypertension or CVD, a personal history of gestational diabetes (GDM) or glucose intolerance, non-Caucasian ethnicity, a sedentary lifestyle, overweight/obesity (defined as BMI > 25 kg/m² or waist circumference > 40 inches in men and > 35 inches in women) and age > 40 years (9).

The International Diabetes Federation (IDF) aimed to create a straightforward, clinically useful definition to identify individuals in any country worldwide at high risk of CVD and diabetes and to allow for comparative epidemiologic studies. This resulted in the IDF consensus definition of MetS in 2005 (10). Central obesity, as defined as BMI > 30 kg/m² or if ≤ 30 kg/m² by ethnic specific waist circumference measurements) was a requisite for the syndrome. Additionally, the definition required the presence of two of the following four elements: triglycerides ≥ 150 mg/dL, HDL-C < 40 mg/dL in men or < 50 mg/dL in women, systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, fasting glucose > 100 mg/dL (based on the 2003 ADA definition of IFG) (11) including diabetes and those with a prior diagnosis of or treatment of any of these conditions (10).

In 2005, the American Heart Association (AHA)/ National Heart, Lung and Blood Institute (NHLBI) also suggested criteria for diagnosis of the metabolic syndrome. Their revised definition of the metabolic syndrome was based on the ATP III criteria and required three of any of the five following criteria: elevated waist circumference (≥ 102 cm (40 inches) in males and ≥ 88 cm (35 inches) in females), triglycerides ≥ 150 mg/dL and HDL-C < 40 mg/dL in men and < 50 mg/dL in women, elevated blood pressure ≥ 130/85 mm Hg and elevated fasting glucose > 100 mg/dL (12). As suggested by the IDF, ethnic-specific waist circumferences were taken into account when using this definition. Additionally, impaired fasting glucose was defined as >100 mg/dl, which was also consistent with the IDF guidelines.

Finally, in an effort to provide more consistency in both clinical care and research of patients with MetS, the IDF, NHLBI, AHA, World Heart Federation, and the International Association for the Study of Obesity published a joint statement in 2009 that provided a “harmonized” definition of MetS (13). According to this joint statement, a diagnosis of the MetS is made when any 3 of the 5 following risk factors are present (Table 1): enlarged waist circumference with population-specific and country-specific criteria; elevated triglycerides, defined as ≥ 150 mg/dL, decreased HDL-C, defined as < 40 mg/dL in men and < 50 mg/dL in women, elevated blood pressure, defined as systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg and elevated fasting glucose, defined as blood glucose > 100 mg/dL, with the inclusion of patients taking medication to manage hypertriglyceridemia, low HDL-C, hypertension. and hyperglycemia. This definition is frequently referred to as the current Harmonization definition.

Table 1. Criteria for Diagnosis of the Metabolic Syndrome	
Measure	Categorical Cut-Points
Waist circumference	Population and country specific definitions
Triglycerides *	≥ 150 mg/dL
High Density Lipoprotein Cholesterol (HDL-C)*	Men < 40 mg/dL Women < 50 mg/dL
Blood Pressure*	≥ 130/ ≥85
Fasting Glucose*	≥ 100 mg/dL

*Drug treatment for elevated triglycerides, low HDL-C, elevated blood pressure or elevated glucose are alternate indicators

It is important to note that in the current Harmonization definition, obesity is diagnosed using waist circumference and not BMI as waist circumference has been shown to better correlate with visceral adiposity and insulin resistance as well as the development of T2DM and CVD than does BMI (10,14,15). Subsequent to the establishment of the harmonized definition, waist to height ratio has been demonstrated to be superior to waist circumference and BMI as a screening tool for cardiometabolic risk factors (diabetes, hypertension, cardiovascular disease, and all outcomes) as well as predicting whole-body fat percentage and visceral adipose tissue mass (16,17). It is not clear if the definition of MetS will be revised over time to reflect these new findings. Additionally, in the current Harmonization definition, ethnic-specific waist circumference cut-off values are used, as it has been shown that certain ethnic groups, especially South Asian populations, have higher degrees of visceral adiposity for given waist circumference measurements compared to Europeans (10,13,18).

PREVALENCE

The prevalence of MetS vary greatly depending on criteria used to define MetS, the age, gender, ethnicity and environment of the population being studied and obesity prevalence of the background population studied (25). Regardless of which criteria are used, however, the prevalence of MetS is high and is on the rise in many Western societies(26).

The National Health and Nutrition Examination Survey (NHANES) reported the overall prevalence of MetS in adults (aged ≥ 20 years) in the United States from 2003 to 2012 was 33% with the prevalence increasing with age, a finding that has been seen in other studies (24,25,27,28). The NHANES report indicates the highest prevalence amongst Hispanics followed by non-Hispanic whites and blacks. Other studies have shown that American Indian, Hawaiian, Polynesian, and Filipino populations develop MetS more than individuals of European descent (27,29-33). Urban populations have higher rates of MetS than rural populations (34,35). Similar to trends in Western societies, recent studies demonstrate rising rates of MetS in many developing countries (36,37). The development of these countries, bringing along a higher calorie diet and decreased physical activity, is thought to be largely responsible for the increased rate of MetS that is being observed (26,38,39). In summary, MetS affects a significant number of individuals worldwide.

CLINICAL UTILITY

The clinical utility of a diagnosis of MetS – vs. the individual components - has been studied extensively. Most recently, Pajunen and colleagues compared the predictive ability of various definitions of MetS, namely the WHO, ATP III, IDF and new Harmonization definitions, found that all these definitions of MetS were significant predictors for incident CVD and T2DM. Additionally, the new Harmonization definition

was found to be a better predictor of CVD endpoint than the sum of its components, as well as when compared to the Framingham risk score, but this was not the case for the prediction of T2DM (19). Importantly, extensive, frequently conflicting literature exists examining the ability of the various definitions of MetS to predict outcomes. Further, skeptics argue that making the diagnosis of MetS does not change the clinical management of these patients, as treatment of patients with MetS starts with diet and exercise and most physicians would offer the same recommendations to a patient with any of the individual elements of MetS (20,21).

In an attempt to settle some of the controversy, a WHO Expert Consultation was undertaken in November 2008. The panel concluded that MetS has limited practical utility as a diagnostic or management tool. They determined that MetS should not be applied as a clinical diagnosis, but rather should be considered a pre-morbid condition and that people with established diabetes or known cardiovascular disease should be excluded (22). They also stated that further attempts to redefine it are inappropriate in light of current knowledge and understanding (23). Despite the conclusions of the panel, the diagnosis of MetS is still commonly encountered in clinical practice as well as in the research arena and arguably applies to roughly one-third of the US adult population (24). It also predisposes to a number of serious conditions beyond diabetes and CVD including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), polycystic ovarian syndrome (PCOS), obstructive sleep apnea (OSA), cancer, and many others.

PATHOGENESIS

There are many different factors that contribute to the development of MetS. However, as initially proposed by Reaven, insulin resistance is thought to play a central role in connecting the different components of MetS and adding to the syndrome's development (1,40). Elevated free fatty acids (FFA) and abnormal adipokine profiles can both cause and result in insulin resistance and can manifest as MetS (41). In this section, we will discuss how these factors contribute to the development of the metabolic abnormalities that characterize insulin resistance and MetS.

Insulin Action and Signaling

Through its complex signaling cascades, insulin regulates glucose and fat metabolism. Pancreatic β -cells release insulin in response to increased circulating glucose levels and subsequently decreases plasma glucose concentrations by coordinately suppressing hepatic glucose production from amino acids and other intermediates of metabolism (gluconeogenesis) and glycogen (glycogenolysis), and enhancing glucose uptake into the muscle and adipose tissue by mobilization of the insulin-responsive glucose transporter 4 (GLUT4) (Fig. 1) (42). Through actions on hormone sensitive lipase, nuclear receptor PPAR γ , and fatty acid synthase, insulin inhibits lipolysis, promotes adipogenesis and adipose tissue differentiation, and under conditions of chronic hyperinsulinemia paradoxically increases fatty acid synthase(41,43).

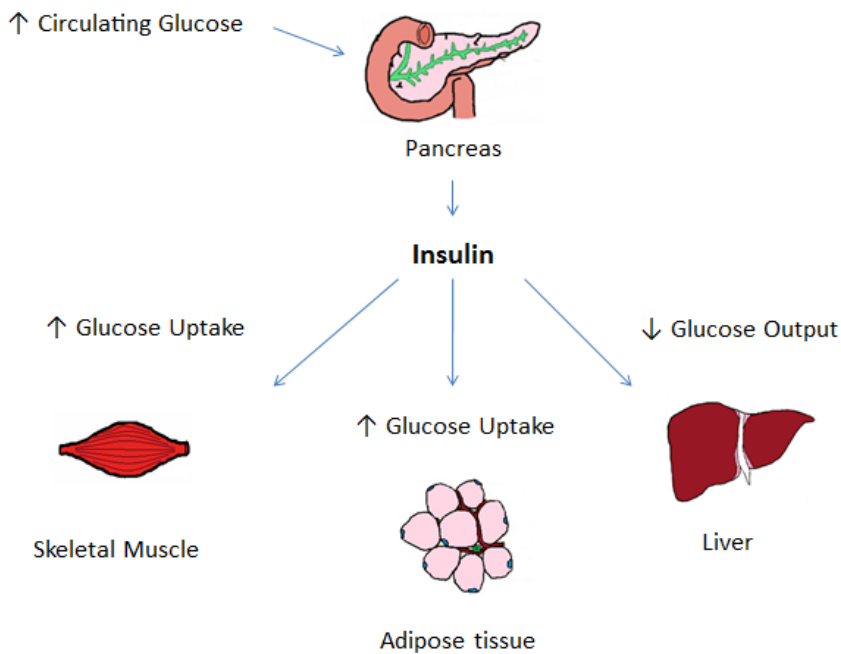


Figure 1: Normal Insulin Action: In individuals with normal insulin sensitivity, the pancreatic β -cells release insulin in response to increased circulating glucose levels (as seen in the postprandial state). Insulin then decreases the plasma glucose concentration by suppressing hepatic glucose output and enhancing glucose uptake into adipose tissue and by skeletal muscle.

Insulin resistance is most simply defined by its end organ effects; a decreased ability of insulin to suppress lipolysis and hepatic glucose production, as well as facilitate glucose uptake from peripheral tissues. There are numerous factors thought to mediate insulin resistance and its adverse effects in MetS. Despite its widespread appreciation in metabolic disease, insulin resistance is still not fully understood and remains an area of intense scientific investigation. In the following section, we will review the ways in which known factors affect insulin resistance in MetS.

It has been thoroughly documented that FFAs mediate many undesirable metabolic effects, especially insulin resistance (44). FFAs are thought to be increased in obesity secondary to increased fat mass. Additionally, under conditions of insulin resistance, insulin's inhibitory effects on lipolysis are reduced, leading to a further increase in FFAs. Increased FFAs are not only a result of insulin resistance, but a cause as well, thus creating a vicious cycle. FFAs can lead to insulin resistance via a variety of mechanisms that include but are not limited to the Randle cycle, the accumulation of intracellular lipid derivatives such as diacylglycerol and ceramides, inflammatory signaling, oxidative stress and mitochondrial dysfunction.

Randle et al. first demonstrated that an elevation in FFA in the diaphragm and heart was associated with an increase in fatty acid oxidation and impaired glucose utilization (45). Via the Randle cycle effect, increased FFAs and fatty acid oxidation lead to increased intracellular glucose content and decreased glucose uptake (46). Studies in rodents and humans have demonstrated that conditions of increased FFA either via lipid infusions or secondary to T2DM lead to impaired glucose uptake and utilization in insulin sensitive tissues (47). This occurs secondary to the inhibition of the insulin signaling pathway.

As FFA levels increase, the capacity of the adipose tissue to take up and store FFAs can be exceeded. When this occurs, FFAs accumulate in tissues with limited ability for lipid storage, such as the liver and skeletal muscle. This phenomenon is known as ectopic fat deposition and is strongly associated with insulin resistance (48). Fatty acids accumulate in myocytes as fatty acid derivatives. Of these fatty acid derivatives, diacylglycerol (DAG), triacylglycerol, and ceramides directly correlate with insulin resistance. DAG interferes with normal insulin signaling by its interaction with a group of novel kinases, members of the protein kinase C family, that serine phosphorylate IRS, thereby impairing tyrosine phosphorylation and activation by insulin (41,48,49). Ceramide activates the enzyme protein phosphatase 2A, leading to dephosphorylation of AKT, thwarting insulin signaling and GLUT4 translocation to the cell membrane. This impairs insulin-mediated glucose uptake into the skeletal muscle (50).

FFAs increase inflammatory signaling pathways through direct interaction with members of the Toll-like receptor (TLR) family and indirectly through the secretion of cytokines, namely tumor necrosis factor- α (TNF- α), and interleukins (IL), IL-1 β and IL-6 (49). TLR are the pathogen recognition receptors of the innate immune system that function to facilitate the detection of microbes and transmit inflammatory signaling (51,52). In vitro, FFA can signal through TLR-2 and TLR-4 on macrophages, thereby inducing pro-inflammatory gene expression (52,53). Studies in mice with a loss of function mutation of the TLR-4 receptor are protected from diet-induced obesity and saturated fatty acid-induced insulin resistance (54). Similarly, animal studies in which TLR-2 is either absent or inhibited, demonstrate a resolution of high fat diet induced insulin resistance (55,56). A recent study in humans corroborates the importance of TLR-2 and TLR-4 in the development of FFA induced insulin resistance. Jialal and colleagues studied individuals with and without MetS (according to the NCEP ATP III definition) and found that those with MetS had increased expression and activity of TLR-2 and TLR-4 (51). TLR-4 activity leads to activation of c-Jun N-terminal kinase (JNK) and I κ B kinase (IKK), which results in degradation of the inhibitor κ B (I κ B α) and activation of Nuclear Factor- κ B (NF- κ B). Through JNK and IKK activation, FFA lead to Ser phosphorylation of IRS-1 and impaired insulin signaling (57,58). Ding and colleagues assessed 1628 Chinese adults and reported that levels of IL-6 and C-reactive protein were significantly associated with MetS (using the Harmonized definition) which also increased concurrent to the increased number of MetS components, further supporting that MetS is a pro-inflammatory state (59).

In obesity, adipose tissue infiltration by macrophages is increased. This leads to a pro-inflammatory state as macrophages produce TNF- α , IL-6 and IL-1 β (60,61). Along with FFA signaling through TLR, these macrophage-derived inflammatory cytokines activate JNK and IKK to further interfere with insulin signaling and action (61). Additionally suppressor of cytokine signaling (SOCS) proteins are induced downstream of these inflammatory cytokines which terminate insulin signaling by promoting the ubiquitination and proteasomal degradation of IRS (62).

Reactive oxygen species (ROS) production increases with fat accumulation. FFAs activate ROS production by adipose tissue by stimulating NADPH oxidase and decreasing the expression of anti-oxidative enzymes (63). When adipose tissues is exposed to oxidative stress, there is a decrease in the anti-inflammatory adipokine, adiponectin (to be discussed in greater detail below) (64). In MetS, there is increased ROS production as a result of elevated levels of inflammatory cytokines and decreased levels of adiponectin (65). Increased levels of ROS lead to hindered insulin signaling by inducing IRS phosphorylation and impairing GLUT4 translocation and gene transcription (66).

It has been shown that there is a connection between mitochondrial dysfunction and insulin resistance in skeletal muscle that precedes the development of obesity and hyperglycemia. Animal studies demonstrate that mitochondrial number and function are intact, if not increased, under conditions of insulin resistance (67,68). On the other hand, studies in obese, insulin-resistant individuals as well as those with T2DM have skeletal muscle mitochondria that are fewer in size as well as number. It has also been shown that these individuals exhibit down-regulation of the genes involved in mitochondrial oxidative phosphorylation, the process by which mitochondria produce energy in the form of ATP (69-72). Studies demonstrate that PPAR γ coactivator-1 α (PGC-1 α), a transcriptional activator involved in mitochondrial biosynthesis, has diminished expression in patients with T2DM, obesity, or a family history of T2DM (73,74). Increased FFA uptake and their incomplete oxidation have also been implicated in mediating mitochondrial dysfunction in the skeletal muscle under insulin resistant conditions (75). Furthermore, mitochondrial dysfunction leads to increased oxidative stress and the formation of ROS, which further diminishes mitochondrial mass and function.

As discussed above, increased FFAs in obesity and MetS are thought to lead to insulin resistance via several different mechanisms. These different mechanisms are not exclusive of one another and interact in such a way as to create a vicious cycle of insulin resistance.

Adipokines

Adipose tissue is an active endocrine organ that releases adipokines, bioactive mediators that affect metabolism (76). It has been demonstrated that individuals with MetS have an abnormal adipokine profile that affects insulin sensitivity (77).

Adiponectin differs from other adipokines in that its level is inversely correlated with body adiposity and insulin resistance (78). The administration of recombinant adiponectin ameliorates insulin resistance in obese mice (78). Adiponectin transgenic mice demonstrate improvements in insulin sensitivity (79). Adiponectin increases insulin secretion in vivo and in vitro (80). In addition to its ability to improve insulin sensitivity in peripheral tissues, adiponectin has been shown to have effects on the central nervous system that affect food intake and energy expenditure (81). In humans, low levels of adiponectin have been strongly associated with insulin resistance, increased body adiposity, T2DM, and MetS (76). Genetic hypoadiponectinemia caused by a missense mutation leads to an increased propensity toward MetS (82). Longitudinal studies demonstrate that in individuals at high risk for developing T2DM, those with higher levels of adiponectin were less likely to develop T2DM than those with lower levels of adiponectin (83). Adiponectin levels have even been proposed to be used as a cut-off for managing the risk of developing MetS in a study of male Japanese workers. In a 3-year prospective cohort study, the risk of developing MetS, calculated by the accelerated failure-time model, demonstrated that the mean time to develop MetS declined with decreasing total adiponectin levels.

Adiponectin modulates glucose metabolism through its interaction with its receptors, the adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2). Binding of adiponectin to AdipoR1 and AdipoR2 results in the activation of signaling pathways affecting glucose and fatty acid metabolism. As a result of adiponectin signaling, AMP-activated protein kinase (AMPK) is phosphorylated, leading to increased glucose uptake in the muscle and reduced gluconeogenesis (84). Adiponectin also has anti-inflammatory actions, suppressing TNF- α and IL-6 expression and anti-atherogenic effects, decreasing levels of pro-atherogenic small, dense low-density lipoprotein (LDL) and TG levels (76,85).

In patients with insulin resistance, there is reduced responsiveness of the skeletal muscle, liver and adipose tissue to insulin. Insulin levels rise in an attempt to maintain euglycemia, and the result is hyperinsulinemia. Hyperinsulinemia has been shown to down-regulate the bioactive high-molecular weight form of adiponectin (86). Thus, the hyperinsulinemia in insulin resistance may decrease adiponectin further contributing to insulin resistance (77). Aside from the direct effects of insulin, changes that characterize the metabolic milieu of insulin resistance such as inflammation, oxidative stress and mitochondrial dysfunction have been shown to suppress adiponectin (77). This relationship is observed clinically in the same study by Ding and colleagues, showing a strong inverse association between adiponectin and HOMA-IR and an inverse trend between adiponectin and an increased number of MetS components (59). Hence, the association between insulin resistance and adiponectin appears to be complex and bidirectional. Further studies are necessary to better define this complicated relationship.

Leptin, another important adipokine produced by adipocytes, exerts effects on appetite and energy expenditure. When leptin binds to its receptor, signaling pathways such as the Janus Kinase-Signal Transducers and Activation of Transcription (JAK/STAT) and IRS/PI3K are activated. The result is similar to what is observed when insulin binds the IR, in that anorexigenic pathways (involving POMC) are favored over orexigenic pathways (involving neuropeptides NPY and AgRP) (87). Studies suggest that leptin affects glucose metabolism independently of its effects on food intake. Studies in rodents suggest that leptin stimulated JAK/STAT signaling is important in food intake and energy expenditure while leptin mediated PI3K signaling plays a role in regulating glucose metabolism (88-90).

Leptin also stimulates FFA oxidation in the liver, pancreas and skeletal muscle. Leptin opposes the action of insulin by decreasing insulin's lipogenic effect on the adipocyte and depleting the triglyceride content of adipose tissue without increasing circulating FFA (91-93). Separate from its effects on lipid and glucose metabolism, leptin affects the immune system, by enhancing the production of inflammatory cytokines and by stimulating T-cell proliferation (94).

While the absence of leptin leads to extreme obesity and insulin resistance, most obese individuals are not leptin deficient. Rather, they have increased levels of leptin but are immune to its appetite suppressant effects. This observation has given rise to the concept of leptin resistance in obesity (95). Similarly, elevated leptin levels have been observed in different populations with metabolic syndrome - (96-98). Decreased sensitivity to leptin leads to increased triglyceride accumulation in adipose tissue, muscle, liver and pancreas, resulting in insulin resistance (76). An alternative perspective is the concept of hypothalamic leptin insufficiency, which states that in conditions of hyperleptinemia, the blood brain barrier prevents entry of leptin into the brain resulting in insufficiencies of leptin at important sites in the CNS (99). Regardless of whether the decreased responsiveness to leptin observed in obesity is due to leptin resistance or hypothalamic leptin insufficiency, the ability of leptin to activate hypothalamic signaling is decreased in obesity and insulin resistance (99).

The role of resistin in MetS is not entirely understood. Resistin is an adipokine that has been seen to be increased in rodent models of obesity, leading to impaired insulin action and β -cell dysfunction (100). Resistin is highly associated with insulin resistance and T2DM in animal models (101). Resistin activates SOCS-3, which inhibits IR phosphorylation and downstream signaling proteins, leading to impaired insulin signaling (102). It also inhibits glucose uptake by skeletal muscle and the liver and enhances hepatic gluconeogenesis (101,103). In humans, the relationship of resistin, MetS and its components are not as clear, however associations between the components of MetS have driven an interest in further understanding its potential role. Resistin expression in humans differs from rodents in its low

expression in white adipose tissue and regulation of concentration by peripheral blood mononuclear cells, macrophages and bone marrow cells (104). Its role in the inflammatory pathway has been well described, associated with upregulation of inflammatory cytokines and to induce monocyte-endothelial cell adhesions [127]. However, the role of resistin in insulin resistance has been controversial. (76). Increased resistin levels have been demonstrated in several studies with individuals with MetS but correlations have been more consistent in women than in men (105-107). Hence, more studies are necessary to better determine the role of resistin in MetS.

Retinol Binding Protein-4 (RBP-4) is the vitamin A (retinol) transporter and is secreted from both adipose tissue and liver. RBP-4 has been shown to be increased in the adipose tissue of mice with an adipose-specific knockout of GLUT4 (108). RBP-4 levels are also elevated in humans with obesity, T2DM, impaired glucose intolerance and those with a strong family history of T2DM (109,110). The suggested mechanisms by which RBP4 can mediate insulin resistance include increased gluconeogenesis and impaired insulin action in the liver and muscle (108). However, there are other studies that do not support the relationship of RBP-4 with altered glucose metabolism (111,112). As with all other adipokines, further exploration is necessary to better define the role of RBP-4 in insulin resistance and MetS.

Apelin, omentin and visfatin are other adipokines have been implicated in the pathogenesis of insulin resistance and MetS. However further study is necessary to better define the part they play in this process. Individuals with insulin resistance and MetS exhibit atypical adipokine profiles that not only result from insulin resistance but further contribute to its development and pathogenesis.

Though there are many different factors that contribute to the development of MetS. Insulin resistance, via augmented FFA levels and irregular adipokine patterns, is largely responsible for the pathogenesis of the syndrome.

Gut Microbiota

There has been considerable interest in the gut microbiota and its relationship with inflammation and metabolism. With limited ability to digest polysaccharides, the gut microbiota in mammals represents an important system significant influence on energy harvest and efficiency(113-115).

In fact, mice raised in a germ-free environment, compared to conventionally raised mice, had lower body fat content and, following colonization with intestinal flora, there was an increase in body fat and hepatic triglyceride synthesis as well as the development of insulin resistance, independent of food intake and energy expenditure (113). Beyond alterations in energy harvest, the gut microbiota composition can also drive low level inflammation which has also been found to be a contributor to obesity and the metabolic syndrome (116,117). Interventional experiments with Roux en Y gastric bypass versus sham surgeries with subsequent microbiota transplant have further underscored the relationship of the microbiota with obesity (118). Observational human studies have noted differences in the microbial diversity in lean and obese subjects as well as in those with differences in microbial diversity based upon diet composition (119-121). Similar differences in microbiota composition have been seen in those with and without type 2 diabetes mellitus (122). Furthermore, infusion of microbiota via gastrointestinal probe have demonstrated alterations in insulin sensitivity (123).

The metabolic syndrome is a product of the complex intertwining of inflammation and insulin resistance; with its relationship to both of these, the gut microbiota has been demonstrated to have a strong

influence on metabolic diseases. From observational to experimental data, the microbiota not only offers important insight into pathophysiology but also has the potential as a therapeutic target.

TREATMENT

Lifestyle modification is the foundational intervention in treatment of MetS. The Diabetes Prevention Program demonstrated that lifestyle intervention reduced the incidence of MetS by 41% compared with placebo. The intensive lifestyle intervention involved a healthy low-calorie, low fat diet and moderate physical activity of at least 150 minutes/week, resulting in a weight reduction of 7% (124). The recommended diet should include < 200 mg/day of cholesterol, < 7% saturated fat, with total fat comprising 25-35% of calories, low simple sugars and increased fruits, vegetables and whole grains (12). Smoking cessation should be instituted in all patients with MetS. Additionally, low dose aspirin is recommended in cases of moderate to high cardiovascular risk where no contraindication to aspirin therapy exists (12). For those patients in whom lifestyle intervention is not sufficient to treat their MetS, pharmacotherapy for the treatment of many of the components of MetS is available.

Historically, many of the medications aimed to treat obesity have failed to gain approval or have been removed from the market by the FDA due to side effects and marginal success in weight reduction (125). However, in the last decade, an increasing number of pharmacotherapies have become FDA approved. Currently available FDA-approved pharmacotherapy for obesity includes phentermine, orlistat, phentermine/topiramate, lorcaserin, bupropion/naltrexone and liraglutide 3.0 mg. Further, individuals with morbid obesity (BMI > 40 kg/m² or >35 kg/m² with comorbidities) may be candidates for bariatric surgery (126). Bariatric surgery has been demonstrated to be an effective treatment of obesity with improvements in weight, T2DM, hypertension, hyperlipidemia, and sleep apnea. Resolution rates of each component reported in the literature are variable, the type of surgery highly influential on the resolution of comorbidities (127). Some studies demonstrate superiority of surgical to nonsurgical treatment in weight loss and MetS (128).

There are no pharmacologic agents specifically approved for prediabetes or the prevention of T2DM. In the Diabetes Prevention Program, metformin was shown to lead to weight loss and a 31% decrease in the incidence of T2DM compared to patients receiving placebo (124). It has been suggested that GLP-1 receptor agonists, agents now commonly used in the treatment of established T2DM, may have a role in prevention of T2DM, but more studies are needed. The American Diabetes Association recommends lifestyle modification over medication for the prevention of diabetes. However, they state that metformin therapy may be considered for the prevention of T2DM in individuals with IGT, IFG or HgA1c 5.7-6.4%, especially for those individuals with BMI > 35 kg/m², those aged < 60 years, and those with a prior diagnosis of GDM (129,130).

Elevated blood pressure is first approached with lifestyle modification. If this fails to bring the blood pressure to goal range <140/90 or <130/80 in patients with diabetes or CKD, medication should be added. First line medications include thiazide diuretics in uncomplicated individuals, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in those with diabetes, congestive heart failure or CKD, or beta blockers in individuals with angina (131).

Drug therapy for dyslipidemia is generally approached with the use of HMG Co-A reductase inhibitors (statins). The primary objective in CVD risk reduction is to lower LDL-C values and the drug of choice for this purposes is statins, which have been shown not only to lower LDL-C, but also to modestly raise

HDL-C and lower triglycerides (132). The second targets in lipid improvement to reduce CVD risk are HDL-C and triglycerides. Niacin is effective at raising HDL-C as well as lowering triglycerides and LDL-C. Fibrates are effective at lowering triglycerides but do not have the beneficial effects on HDL-C and LDL-C. Omega-3 polyunsaturated fatty acids (n-3 PUFA) in fish oil can also be used to lower triglycerides with recent data from the REDUCE-IT trial demonstrating a reduced risk of ischemic events in patients with elevated triglycerides despite statin therapy receiving icosapent ethyl.

CONCLUSION

The metabolic syndrome is a collection of related risk factors that predispose an individual to the development of T2DM and CVD. It affects a large number of people worldwide and its prevalence is increasing. The diagnostic criteria for MetS have been harmonized for the purpose of providing more consistency in clinical care and research of patients with MetS. Insulin resistance remains at the core of the syndrome, as it did when it was first introduced by Reaven in 1988, and appears to contribute to the development of MetS, via elevated FFA levels and abnormal adipokine profiles. Insulin resistance has both metabolic and mitogenic effects and can result in the development of hyperglycemia and T2DM, hypertension, dyslipidemia, NAFLD, PCOS, OSA, sexual dysfunction, and cancer. In patients with MetS, lifestyle modification is imperative in decreasing the risk of CVD and treating many of the associated conditions. Treatment of the individual conditions is often also required.

REFERENCES

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37(12):1595-1607.
2. Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. *Annu Rev Med*. 1993;44:121-131.
3. Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven G. Relationship between degree of obesity and in vivo insulin action in man. *Am J Physiol*. 1985;248(3 Pt 1):E286-291.
4. Reaven GM. Banting Lecture 1988. Role of insulin resistance in human disease. 1988. *Nutrition*. 1997;13(1):65; discussion 64, 66.
5. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15(7):539-553.
6. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabet Med*. 1999;16(5):442-443.
7. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-2497.
8. Eisenmann JC. On the use of a continuous metabolic syndrome score in pediatric research. *Cardiovasc Diabetol*. 2008;7:17.
9. Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, Handelsman Y, Hellman R, Jellinger PS, Kendall D, Krauss RM, Neufeld ND, Petak SM, Rodbard HW, Seibel JA, Smith DA, Wilson PW. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract*. 2003;9(3):237-252.
10. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. *Lancet*. 2005;366(9491):1059-1062.

11. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2003;26 Suppl 1:S5-20.
12. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr., Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112(17):2735-2752.
13. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC, Jr. 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):1640-1645.
14. Ohlson LO, Larsson B, Svardsudd K, Welin L, Eriksson H, Wilhelmsen L, Bjorntorp P, Tibblin G. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes*. 1985;34(10):1055-1058.
15. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P, Jr., Razak F, Sharma AM, Anand SS. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet*. 2005;366(9497):1640-1649.
16. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obes Rev*. 2012;13(3):275-286.
17. Swainson MG, Batterham AM, Tsakirides C, Rutherford ZH, Hind K. Prediction of whole-body fat percentage and visceral adipose tissue mass from five anthropometric variables. *PLoS One*. 2017;12(5):e0177175.
18. Lear SA, Humphries KH, Kohli S, Birmingham CL. The use of BMI and waist circumference as surrogates of body fat differs by ethnicity. *Obesity (Silver Spring)*. 2007;15(11):2817-2824.
19. Pajunen P, Rissanen H, Harkanen T, Jula A, Reunanen A, Salomaa V. The metabolic syndrome as a predictor of incident diabetes and cardiovascular events in the Health 2000 Study. *Diabetes Metab*. 2010;36(5):395-401.
20. Gale EA. Should we dump the metabolic syndrome? Yes. *BMJ*. 2008;336(7645):640.
21. Kahn R. Metabolic syndrome--what is the clinical usefulness? *Lancet*. 2008;371(9628):1892-1893.
22. Beltran-Sanchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999-2010. *J Am Coll Cardiol*. 2013;62(8):697-703.
23. Simmons RK, Alberti KG, Gale EA, Colagiuri S, Tuomilehto J, Qiao Q, Ramachandran A, Tajima N, Brajkovich Mirchov I, Ben-Nakhi A, Reaven G, Hama Sambo B, Mendis S, Roglic G. The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. *Diabetologia*. 2010;53(4):600-605.
24. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003-2012. *JAMA*. 2015;313(19):1973-1974.
25. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H, Eckel RH. The metabolic syndrome. *Endocr Rev*. 2008;29(7):777-822.
26. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. *BMC Med*. 2011;9:48.
27. Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. *Endocrinol Metab Clin North Am*. 2004;33(2):351-375, table of contents.

28. Ford ES, Li C, Zhao G. Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. *J Diabetes*. 2010;2(3):180-193.
29. Araneta MR, Wingard DL, Barrett-Connor E. Type 2 diabetes and metabolic syndrome in Filipina-American women: a high-risk nonobese population. *Diabetes Care*. 2002;25(3):494-499.
30. Maggi S, Noale M, Gallina P, Bianchi D, Marzari C, Limongi F, Crepaldi G. Metabolic syndrome, diabetes, and cardiovascular disease in an elderly Caucasian cohort: the Italian Longitudinal Study on Aging. *J Gerontol A Biol Sci Med Sci*. 2006;61(5):505-510.
31. Mancina G, Bombelli M, Corrao G, Facchetti R, Madotto F, Giannattasio C, Trevano FQ, Grassi G, Zanchetti A, Sega R. Metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study: daily life blood pressure, cardiac damage, and prognosis. *Hypertension*. 2007;49(1):40-47.
32. Simmons D, Thompson CF. Prevalence of the metabolic syndrome among adult New Zealanders of Polynesian and European descent. *Diabetes Care*. 2004;27(12):3002-3004.
33. Welty TK, Lee ET, Yeh J, Cowan LD, Go O, Fabsitz RR, Le NA, Oopik AJ, Robbins DC, Howard BV. Cardiovascular disease risk factors among American Indians. The Strong Heart Study. *Am J Epidemiol*. 1995;142(3):269-287.
34. Feng Y, Hong X, Li Z, Zhang W, Jin D, Liu X, Zhang Y, Hu FB, Wei LJ, Zang T, Xu X. Prevalence of metabolic syndrome and its relation to body composition in a Chinese rural population. *Obesity (Silver Spring)*. 2006;14(11):2089-2098.
35. Lorenzo C, Serrano-Rios M, Martinez-Larrad MT, Gonzalez-Sanchez JL, Seclen S, Villena A, Gonzalez-Villalpando C, Williams K, Haffner SM. Geographic variations of the International Diabetes Federation and the National Cholesterol Education Program-Adult Treatment Panel III definitions of the metabolic syndrome in nondiabetic subjects. *Diabetes Care*. 2006;29(3):685-691.
36. Azimi-Nezhad M, Herbeth B, Siest G, Dade S, Ndiaye NC, Esmaily H, Hosseini SJ, Ghayour-Mobarhan M, Visvikis-Siest S. High Prevalence of Metabolic Syndrome in Iran in Comparison with France: What Are the Components That Explain This? *Metab Syndr Relat Disord*. 2012.
37. Pandit K, Goswami S, Ghosh S, Mukhopadhyay P, Chowdhury S. Metabolic syndrome in South Asians. *Indian J Endocrinol Metab*. 2012;16(1):44-55.
38. McKeigue PM, Ferrie JE, Pierpoint T, Marmot MG. Association of early-onset coronary heart disease in South Asian men with glucose intolerance and hyperinsulinemia. *Circulation*. 1993;87(1):152-161.
39. Thomas GN, Ho SY, Janus ED, Lam KS, Hedley AJ, Lam TH. The US National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) prevalence of the metabolic syndrome in a Chinese population. *Diabetes Res Clin Pract*. 2005;67(3):251-257.
40. Smith DO, LeRoith D. Insulin resistance syndrome, pre-diabetes, and the prevention of type 2 diabetes mellitus. *Clin Cornerstone*. 2004;6(2):7-6.
41. Gallagher EJ, Leroith D, Karnieli E. The metabolic syndrome--from insulin resistance to obesity and diabetes. *Med Clin North Am*. 2011;95(5):855-873.
42. Karnieli E, Zarnowski MJ, Hissin PJ, Simpson IA, Salans LB, Cushman SW. Insulin-stimulated translocation of glucose transport systems in the isolated rat adipose cell. Time course, reversal, insulin concentration dependency, and relationship to glucose transport activity. *J Biol Chem*. 1981;256(10):4772-4777.
43. Najjar SM, Yang Y, Fernstrom MA, Lee SJ, Deangelis AM, Rjaily GA, Al-Share QY, Dai T, Miller TA, Ratnam S, Ruch RJ, Smith S, Lin SH, Beauchemin N, Oyarce AM. Insulin acutely decreases hepatic fatty acid synthase activity. *Cell Metab*. 2005;2(1):43-53.

44. Karpe F, Dickmann JR, Frayn KN. Fatty acids, obesity, and insulin resistance: time for a reevaluation. *Diabetes*. 2011;60(10):2441-2449.
45. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet*. 1963;1(7285):785-789.
46. Randle PJ. Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. *Diabetes Metab Rev*. 1998;14(4):263-283.
47. Boden G, Jadali F, White J, Liang Y, Mozzoli M, Chen X, Coleman E, Smith C. Effects of fat on insulin-stimulated carbohydrate metabolism in normal men. *J Clin Invest*. 1991;88(3):960-966.
48. Yki-Jarvinen H. Ectopic fat accumulation: an important cause of insulin resistance in humans. *J R Soc Med*. 2002;95 Suppl 42:39-45.
49. Martins AR, Nachbar RT, Gorjao R, Vinolo MA, Festuccia WT, Lambertucci RH, Cury-Boaventura MF, Silveira LR, Curi R, Hirabara SM. Mechanisms underlying skeletal muscle insulin resistance induced by fatty acids: importance of the mitochondrial function. *Lipids Health Dis*. 2012;11:30.
50. Summers SA. Sphingolipids and insulin resistance: the five Ws. *Curr Opin Lipidol*. 2010;21(2):128-135.
51. Jialal I, Huet BA, Kaur H, Chien A, Devaraj S. Increased toll-like receptor activity in patients with metabolic syndrome. *Diabetes Care*. 2012;35(4):900-904.
52. Nguyen MT, Favelyukis S, Nguyen AK, Reichart D, Scott PA, Jenn A, Liu-Bryan R, Glass CK, Neels JG, Olefsky JM. A subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via Toll-like receptors 2 and 4 and JNK-dependent pathways. *J Biol Chem*. 2007;282(48):35279-35292.
53. 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):3015-3025.
54. Tsukumo DM, Carvalho-Filho MA, Carvalheira JB, Prada PO, Hirabara SM, Schenka AA, Araujo EP, Vassallo J, Curi R, Velloso LA, Saad MJ. Loss-of-function mutation in Toll-like receptor 4 prevents diet-induced obesity and insulin resistance. *Diabetes*. 2007;56(8):1986-1998.
55. Caricilli AM, Nascimento PH, Pauli JR, Tsukumo DM, Velloso LA, Carvalheira JB, Saad MJ. Inhibition of toll-like receptor 2 expression improves insulin sensitivity and signaling in muscle and white adipose tissue of mice fed a high-fat diet. *J Endocrinol*. 2008;199(3):399-406.
56. Ehses JA, Meier DT, Wueest S, Rytka J, Boller S, Wielinga PY, Schraenen A, Lemaire K, Debray S, Van Lommel L, Pospisilik JA, Tschopp O, Schultze SM, Malipiero U, Esterbauer H, Ellingsgaard H, Rutti S, Schuit FC, Lutz TA, Boni-Schnetzler M, Konrad D, Donath MY. Toll-like receptor 2-deficient mice are protected from insulin resistance and beta cell dysfunction induced by a high-fat diet. *Diabetologia*. 2010;53(8):1795-1806.
57. Bhargava P, Lee CH. Role and function of macrophages in the metabolic syndrome. *Biochem J*. 2012;442(2):253-262.
58. Hotamisligil GS. Inflammation and endoplasmic reticulum stress in obesity and diabetes. *Int J Obes (Lond)*. 2008;32 Suppl 7:S52-54.
59. Ding Y, Li S, Ma RL, Guo H, Zhang J, Zhang M, Liu J, Guo S. Association of homeostasis model assessment of insulin resistance, adiponectin, and low-grade inflammation with the course of the metabolic syndrome. *Clin Biochem*. 2015.
60. 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):1796-1808.
61. 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):408-417.

62. Lebrun P, Van Obberghen E. SOCS proteins causing trouble in insulin action. *Acta Physiol (Oxf)*. 2008;192(1):29-36.
63. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, Nakayama O, Makishima M, Matsuda M, Shimomura I. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest*. 2004;114(12):1752-1761.
64. Soares AF, Guichardant M, Cozzone D, Bernoud-Hubac N, Bouzaidi-Tiali N, Lagarde M, Geloën A. Effects of oxidative stress on adiponectin secretion and lactate production in 3T3-L1 adipocytes. *Free Radic Biol Med*. 2005;38(7):882-889.
65. Otani H. Oxidative stress as pathogenesis of cardiovascular risk associated with metabolic syndrome. *Antioxid Redox Signal*. 2011;15(7):1911-1926.
66. Bloch-Damti A, Bashan N. Proposed mechanisms for the induction of insulin resistance by oxidative stress. *Antioxid Redox Signal*. 2005;7(11-12):1553-1567.
67. 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):7815-7820.
68. Holloway GP, Gurd BJ, Snook LA, Lally J, Bonen A. Compensatory increases in nuclear PGC1alpha protein are primarily associated with subsarcolemmal mitochondrial adaptations in ZDF rats. *Diabetes*. 2010;59(4):819-828.
69. Hojlund K, Mogensen M, Sahlin K, Beck-Nielsen H. Mitochondrial dysfunction in type 2 diabetes and obesity. *Endocrinol Metab Clin North Am*. 2008;37(3):713-731, x.
70. Kim JA, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin resistance. *Circ Res*. 2008;102(4):401-414.
71. Chomentowski P, Coen PM, Radikova Z, Goodpaster BH, Toledo FG. Skeletal muscle mitochondria in insulin resistance: differences in intermyofibrillar versus subsarcolemmal subpopulations and relationship to metabolic flexibility. *J Clin Endocrinol Metab*. 2011;96(2):494-503.
72. Coletta DK, Mandarino LJ. Mitochondrial dysfunction and insulin resistance from the outside in: extracellular matrix, the cytoskeleton, and mitochondria. *Am J Physiol Endocrinol Metab*. 2011;301(5):E749-755.
73. Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, Miyazaki Y, Kohane I, Costello M, Saccone R, Landaker EJ, Goldfine AB, Mun E, DeFronzo R, Finlayson J, Kahn CR, Mandarino LJ. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1. *Proc Natl Acad Sci U S A*. 2003;100(14):8466-8471.
74. Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstrale M, Laurila E, Houstis N, Daly MJ, Patterson N, Mesirov JP, Golub TR, Tamayo P, Spiegelman B, Lander ES, Hirschhorn JN, Altshuler D, Groop LC. PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nat Genet*. 2003;34(3):267-273.
75. Koves TR, Ussher JR, Noland RC, Slentz D, Mosedale M, Ilkayeva O, Bain J, Stevens R, Dyck JR, Newgard CB, Lopaschuk GD, Muoio DM. Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. *Cell Metab*. 2008;7(1):45-56.
76. Rabe K, Lehrke M, Parhofer KG, Broedl UC. Adipokines and insulin resistance. *Mol Med*. 2008;14(11-12):741-751.
77. Deng Y, Scherer PE. Adipokines as novel biomarkers and regulators of the metabolic syndrome. *Ann N Y Acad Sci*. 2010;1212:E1-E19.
78. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H,

- Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nat Med.* 2001;7(8):941-946.
79. Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, Uchida S, Ito Y, Takakuwa K, Matsui J, Takata M, Eto K, Terauchi Y, Komeda K, Tsunoda M, Murakami K, Ohnishi Y, Naitoh T, Yamamura K, Ueyama Y, Froguel P, Kimura S, Nagai R, Kadowaki T. Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. *J Biol Chem.* 2003;278(4):2461-2468.
80. Okamoto M, Ohara-Imaizumi M, Kubota N, Hashimoto S, Eto K, Kanno T, Kubota T, Wakui M, Nagai R, Noda M, Nagamatsu S, Kadowaki T. Adiponectin induces insulin secretion in vitro and in vivo at a low glucose concentration. *Diabetologia.* 2008;51(5):827-835.
81. Kubota N, Yano W, Kubota T, Yamauchi T, Itoh S, Kumagai H, Kozono H, Takamoto I, Okamoto S, Shiuchi T, Suzuki R, Satoh H, Tsuchida A, Moroi M, Sugi K, Noda T, Ebinuma H, Ueta Y, Kondo T, Araki E, Ezaki O, Nagai R, Tobe K, Terauchi Y, Ueki K, Minokoshi Y, Kadowaki T. Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. *Cell Metab.* 2007;6(1):55-68.
82. Kondo H, Shimomura I, Matsukawa Y, Kumada M, Takahashi M, Matsuda M, Ouchi N, Kihara S, Kawamoto T, Sumitsuji S, Funahashi T, Matsuzawa Y. Association of adiponectin mutation with type 2 diabetes: a candidate gene for the insulin resistance syndrome. *Diabetes.* 2002;51(7):2325-2328.
83. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, Krakoff J. Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet.* 2002;360(9326):57-58.
84. Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, Okada-Iwabu M, Kawamoto S, Kubota N, Kubota T, Ito Y, Kamon J, Tsuchida A, Kumagai K, Kozono H, Hada Y, Ogata H, Tokuyama K, Tsunoda M, Ide T, Murakami K, Awazawa M, Takamoto I, Froguel P, Hara K, Tobe K, Nagai R, Ueki K, Kadowaki T. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med.* 2007;13(3):332-339.
85. Gallagher EJ, Leroith D, Karnieli E. Insulin resistance in obesity as the underlying cause for the metabolic syndrome. *Mt Sinai J Med.* 2010;77(5):511-523.
86. Basu R, Pajvani UB, Rizza RA, Scherer PE. Selective downregulation of the high molecular weight form of adiponectin in hyperinsulinemia and in type 2 diabetes: differential regulation from nondiabetic subjects. *Diabetes.* 2007;56(8):2174-2177.
87. Prodi E, Obici S. Minireview: the brain as a molecular target for diabetic therapy. *Endocrinology.* 2006;147(6):2664-2669.
88. Bates SH, Kulkarni RN, Seifert M, Myers MG, Jr. Roles for leptin receptor/STAT3-dependent and -independent signals in the regulation of glucose homeostasis. *Cell Metab.* 2005;1(3):169-178.
89. Coppari R, Ichinose M, Lee CE, Pullen AE, Kenny CD, McGovern RA, Tang V, Liu SM, Ludwig T, Chua SC, Jr., Lowell BB, Elmquist JK. The hypothalamic arcuate nucleus: a key site for mediating leptin's effects on glucose homeostasis and locomotor activity. *Cell Metab.* 2005;1(1):63-72.
90. Morton GJ, Gelling RW, Niswender KD, Morrison CD, Rhodes CJ, Schwartz MW. Leptin regulates insulin sensitivity via phosphatidylinositol-3-OH kinase signaling in mediobasal hypothalamic neurons. *Cell Metab.* 2005;2(6):411-420.
91. Buettner C, Muse ED, Cheng A, Chen L, Scherer T, Poci A, Su K, Cheng B, Li X, Harvey-White J, Schwartz GJ, Kunos G, Rossetti L. Leptin controls adipose tissue lipogenesis via central, STAT3-independent mechanisms. *Nat Med.* 2008;14(6):667-675.

92. Lago F, Gomez R, Gomez-Reino JJ, Dieguez C, Gualillo O. Adipokines as novel modulators of lipid metabolism. *Trends Biochem Sci.* 2009;34(10):500-510.
93. Shimabukuro M, Koyama K, Chen G, Wang MY, Trieu F, Lee Y, Newgard CB, Unger RH. Direct antidiabetic effect of leptin through triglyceride depletion of tissues. *Proc Natl Acad Sci U S A.* 1997;94(9):4637-4641.
94. Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. *J Clin Endocrinol Metab.* 2008;93(11 Suppl 1):S64-73.
95. Munzberg H, Myers MG, Jr. Molecular and anatomical determinants of central leptin resistance. *Nat Neurosci.* 2005;8(5):566-570.
96. Yun JE, Kimm H, Jo J, Jee SH. Serum leptin is associated with metabolic syndrome in obese and nonobese Korean populations. *Metabolism.* 2010;59(3):424-429.
97. Lee SW, Jo HH, Kim MR, You YO, Kim JH. Association between metabolic syndrome and serum leptin levels in postmenopausal women. *J Obstet Gynaecol.* 2012;32(1):73-77.
98. Yoshinaga M, Sameshima K, Tanaka Y, Wada A, Hashiguchi J, Tahara H, Kono Y. Adipokines and the prediction of the accumulation of cardiovascular risk factors or the presence of metabolic syndrome in elementary school children. *Circ J.* 2008;72(11):1874-1878.
99. Kalra SP. Central leptin insufficiency syndrome: an interactive etiology for obesity, metabolic and neural diseases and for designing new therapeutic interventions. *Peptides.* 2008;29(1):127-138.
100. Gao CL, Zhao DY, Qiu J, Zhang CM, Ji CB, Chen XH, Liu F, Guo XR. Resistin induces rat insulinoma cell RINm5F apoptosis. *Mol Biol Rep.* 2009;36(7):1703-1708.
101. Yang Y, Xiao M, Mao Y, Li H, Zhao S, Gu Y, Wang R, Yu J, Zhang X, Irwin DM, Niu G, Tan H. Resistin and insulin resistance in hepatocytes: resistin disturbs glycogen metabolism at the protein level. *Biomed Pharmacother.* 2009;63(5):366-374.
102. Steppan CM, Wang J, Whitman EL, Birnbaum MJ, Lazar MA. Activation of SOCS-3 by resistin. *Mol Cell Biol.* 2005;25(4):1569-1575.
103. Banerjee RR, Rangwala SM, Shapiro JS, Rich AS, Rhoades B, Qi Y, Wang J, Rajala MW, Poci A, Scherer PE, Steppan CM, Ahima RS, Obici S, Rossetti L, Lazar MA. Regulation of fasted blood glucose by resistin. *Science.* 2004;303(5661):1195-1198.
104. Abate N, Sallam HS, Rizzo M, Nikolic D, Obradovic M, Bjelogrić P, Isenovic ER. Resistin: an inflammatory cytokine. Role in cardiovascular diseases, diabetes and the metabolic syndrome. *Curr Pharm Des.* 2014;20(31):4961-4969.
105. Malo E, Ukkola O, Jokela M, Moilanen L, Kahonen M, Nieminen MS, Salomaa V, Jula A, Kesaniemi YA. Resistin is an indicator of the metabolic syndrome according to five different definitions in the Finnish Health 2000 survey. *Metab Syndr Relat Disord.* 2011;9(3):203-210.
106. Norata GD, Ongari M, Garlaschelli K, Raselli S, Grigore L, Catapano AL. Plasma resistin levels correlate with determinants of the metabolic syndrome. *Eur J Endocrinol.* 2007;156(2):279-284.
107. Singh AK, Tiwari S, Gupta A, Natu SM, Mittal B, Pant AB. Association of Resistin with Metabolic Syndrome in Indian Subjects. *Metab Syndr Relat Disord.* 2012.
108. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, Kotani K, Quadro L, Kahn BB. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature.* 2005;436(7049):356-362.
109. 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):2552-2563.
110. Meisinger C, Ruckert IM, Rathmann W, Doring A, Thorand B, Huth C, Kowall B, Koenig W. Retinol-binding protein 4 is associated with prediabetes in adults from the general population: the

Cooperative Health Research in the Region of Augsburg (KORA) F4 Study. *Diabetes Care*. 2011;34(7):1648-1650.

111. Janke J, Engeli S, Boschmann M, Adams F, Bohnke J, Luft FC, Sharma AM, Jordan J. Retinol-binding protein 4 in human obesity. *Diabetes*. 2006;55(10):2805-2810.
112. Promintzer M, Krebs M, Todoric J, Luger A, Bischof MG, Nowotny P, Wagner O, Esterbauer H, Anderwald C. Insulin resistance is unrelated to circulating retinol binding protein and protein C inhibitor. *J Clin Endocrinol Metab*. 2007;92(11):4306-4312.
113. Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A*. 2004;101(44):15718-15723.
114. Turnbaugh PJ, Gordon JI. The core gut microbiome, energy balance and obesity. *J Physiol*. 2009;587(Pt 17):4153-4158.
115. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006;444(7122):1027-1031.
116. Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE, Gewirtz AT. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science*. 2010;328(5975):228-231.
117. Chassaing B, Gewirtz AT. Gut microbiota, low-grade inflammation, and metabolic syndrome. *Toxicol Pathol*. 2014;42(1):49-53.
118. Liou AP, Paziuk M, Luevano JM, Jr., Machineni S, Turnbaugh PJ, Kaplan LM. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. *Sci Transl Med*. 2013;5(178):178ra141.
119. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G, Lionetti P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci U S A*. 2010;107(33):14691-14696.
120. Turnbaugh PJ, Hamady M, Yatsunencko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI. A core gut microbiome in obese and lean twins. *Nature*. 2009;457(7228):480-484.
121. Schwartz A, Taras D, Schafer K, Beijer S, Bos NA, Donus C, Hardt PD. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity (Silver Spring)*. 2010;18(1):190-195.
122. Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sorensen SJ, Hansen LH, Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One*. 2010;5(2):e9085.
123. Vrieze A, Van Nood E, Holleman F, Salojarvi J, Kootte RS, Bartelsman JF, Dallinga-Thie GM, Ackermans MT, Serlie MJ, Oozeer R, Derrien M, Druesne A, Van Hylckama Vlieg JE, Bloks VW, Groen AK, Heilig HG, Zoetendal EG, Stroes ES, de Vos WM, Hoekstra JB, Nieuwdorp M. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology*. 2012;143(4):913-916 e917.
124. Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, Fowler S. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med*. 2005;142(8):611-619.
125. Leroith D. Pathophysiology of the metabolic syndrome: implications for the cardiometabolic risks associated with type 2 diabetes. *Am J Med Sci*. 2012;343(1):13-16.
126. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrenbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. *JAMA*. 2004;292(14):1724-1737.
127. Shuai X, Tao K, Mori M, Kanda T. Bariatric surgery for metabolic syndrome in obesity. *Metab Syndr Relat Disord*. 2015;13(4):149-160.

128. O'Brien PE, Dixon JB, Laurie C, Skinner S, Proietto J, McNeil J, Strauss B, Marks S, Schachter L, Chapman L, Anderson M. Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: a randomized trial. *Ann Intern Med*. 2006;144(9):625-633.
129. Executive summary: Standards of medical care in diabetes--2012. *Diabetes Care*. 2012;35 Suppl 1:S4-S10.
130. American Diabetes A. (5) Prevention or delay of type 2 diabetes. *Diabetes Care*. 2015;38 Suppl:S31-32.
131. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206-1252.
132. Onat A. Metabolic syndrome: nature, therapeutic solutions and options. *Expert Opin Pharmacother*. 2011;12(12):1887-1900.

