Insulin Resistance in Obesity as the Underlying Cause for the Metabolic Syndrome

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OUTLINE

ABSTRACT

The metabolic syndrome affects more than a third of the US population, predisposing to the development of type 2 diabetes and cardiovascular disease. The 2009 consensus statement from the International Diabetes Federation, American Heart Association, World Heart Federation, International Atherosclerosis Society, International Association for the Study of Obesity, and the National Heart, Lung, and Blood Institute defines the metabolic syndrome as 3 of the following elements: abdominal obesity, elevated blood pressure, elevated triglycerides, low high-density lipoprotein cholesterol, and hyperglycemia. Many factors contribute to this syndrome, including decreased physical activity, genetic predisposition, chronic inflammation, free fatty acids, and mitochondrial dysfunction. Insulin resistance appears to be the common link between these elements, obesity and the metabolic syndrome. In normal circumstances, insulin stimulates glucose uptake into skeletal muscle, inhibits hepatic gluconeogenesis, and decreases adipose-tissue lipolysis and hepatic production of very-low-density lipoproteins. Insulin signaling in the brain decreases appetite and prevents glucose production by the liver through neuronal signals from the hypothalamus. Insulin resistance, in contrast, leads to the release of free fatty acids from adipose tissue, increased hepatic production of very-low-density lipoproteins and decreased high-density lipoproteins. Increased production of free fatty acids, inflammatory cytokines, and adipokines and mitochondrial dysfunction contribute to impaired insulin signaling, decreased skeletal muscle glucose uptake, increased hepatic gluconeogenesis, and β cell dysfunction, leading to hyperglycemia. In addition, insulin resistance leads to the development of hypertension by impairing vasodilation induced by nitric oxide. In this review, we discuss normal insulin signaling and the mechanisms by which insulin resistance contributes to the development of the metabolic syndrome. ***Mt Sinai J Med 77:511–523, 2010.*** *© 2010 Mount Sinai School of Medicine*

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The metabolic syndrome is a collection of related risk factors that predispose to the development of type 2 diabetes (T2DM) and cardiovascular disease (CVD). The term "metabolic syndrome" was coined by Haller in 1977 to describe the collection of risk factors (obesity, diabetes, hyperlipidemia, hyperuricemia, and steatic hepatosis) that were found in a German population to increase the risk of developing ischemic heart disease.[1] The complications of obesity have been recognized since ancient times; Hippocrates noted that "sudden death is more common in those that are naturally fat than lean," possibly describing cardiac disease

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associated with obesity.[2] The 17th-century Dutch surgeon Nicholas Tulp described the case of a patient with obesity, hypertriglyceridemia, and bleeding, linking obesity with lipid abnormalities and hypertension.[3] Subsequently, in the 18th century, the Italian anatomist Giovanni Battista Morgagni recorded his postmortem findings in 2 patients with visceral adiposity and reported evidence of hypertension, dyslipidemia, and hyperuricemia along with sleep apnea, heart failure, and cerebrovascular disease.[4] The original description of the metabolic syndrome is frequently attributed to the Swedish physician Kylin, who in 1923 described a syndrome of hypertension, dyslipidemia, and hyperuricemia in addition to hyperglycemia.[5] In his Banting lecture in 1988, Reaven described hyperinsulinemia and insulin resistance (IR) as the common thread linking these manifestations and referred to this syndrome as "Syndrome X."[6]

The first formal definition of the metabolic syndrome was proposed by the World Health Organization in 1998; however, this definition was thought to be impractical by many, as it included a hyperinsulinemic euglycemic clamp study as one of the diagnostic criteria for IR.[7] Various other societies including the European Group for the Study of Insulin Resistance, the National Cholesterol Education Program Adult Treatment Panel III (ATP III), the American Association of Clinical Endocrinologists, the International Diabetes Federation (IDF), the American Heart Association (AHA), and the National Heart, Lung, and Blood Institute (NHLBI), have published different definitions of the metabolic syndrome since that time.[8–11] The conflicting definitions have caused uncertainty among physicians as to how to identify patients with the metabolic syndrome and inconsistencies in epidemiological research, depending on what criteria are used. In 2009, the IDF, AHA, NHLBI, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity published a joint statement with a harmonized definition of the metabolic syndrome.[12] According to this statement, any 3 of the following 5 risk factors constitutes a diagnosis of the metabolic syndrome (Table 1): enlarged waist circumference (WC) with different population-specific and country-specific criteria; elevated triglycerides (TG) of ≥1.7 mmol/L (150 mg/dL); reduced high-density lipoprotein (HDL) cholesterol of <1.03 mmol/L (40 mg/dL) in men and <1.29 mmol/L (50 mg/dL) in women; elevated blood pressure, with a systolic blood pressure ≥130 mm Hg or a diastolic blood pressure ≥85 mm Hg; and elevated fasting glucose ≥5.6 mmol/L (100 mg/dL), with the inclusion of those individuals using medication to treat hypertriglyceridemia, decrease HDL, hypertension, or hyperglycemia.[12] The clinical significance of the metabolic syndrome has been examined in prospective studies. A meta-analysis of these studies reported that it carries an increased relative risk (RR) of developing T2DM of 2.99, along with a RR of 1.65 of developing CVD and a RR of 1.27 for all-cause mortality.[13]

Table 1. *Criteria for Diagnosis of the Metabolic Syndrome.*

Increased WC	Cutoff*
Elevated TG or on treatment for elevated TG	≥150 mg/dL
Decreased HDL or on treatment for decreased HDL	Men <40 mg/dL; Women <50 mg/dL
Elevated BP or on treatment for hypertension	Systolic BP ≥130 mm Hg or; diastolic BP ≥85 mm Hg
Elevated FBG	≥100 mg/dL

Abbreviations: BP, blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; NHLBI, National Heart, Lung, and Blood Institute; TG, triglycerides; WC, waist circumference.

* Based on population-specific or country-specific criteria; WC cutoff varies by ethnicity and country. IDF male cutoff measurements are ≥94 cm for Europoid, Middle Eastern, and sub-Saharan African populations; and ≥90 cm for Asian and Central and South American populations. IDF female cutoff measurements are ≥80 cm for all populations. NHLBI recommended cutoff is ≥102 cm for US males and ≥88 cm for US females.[12]

A meta-analysis of prospective studies concerning the metabolic syndrome has shown that it carries an increased relative risk of developing type 2 diabetes mellitus of 2.99, along with a relative risk of 1.65 of developing cardiovascular disease and a relative risk of 1.27 for all-cause mortality.

Significant controversy surroundes the metabolic syndrome, its definitions, and clinical value. Those who oppose its existence as a clinical syndrome question the evidence that has led to the cutoff values that define the metabolic syndrome. They object to it being called a syndrome, given that it does not have a single clear etiology. In addition, they argue that the syndrome adds little to the traditional Framingham risk factors for predicting

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the development of CVD and suggest that a fasting glucose may offer as much information about the risk of developing subsequent diabetes as the more complex components of the metabolic syndrome. Finally, they propose that it does not enhance the clinical management of these patients, in that the treatment guidelines for the metabolic syndrome begin with diet and exercise, so they query whether a physician would not offer the same advice to any patient with any one of the individual components of the metabolic syndrome.[14,15] However, some studies have suggested that up to 40% of obese individuals may be metabolically normal and may not be at greater risk of developing T2DM or CVD.[16,17] Therefore, diagnosing the metabolic syndrome and giving it a label emphasizes the importance of assessing multiple risk factors in patients and highlights the importance of lifestyle interventions.[18] One recent large study, the National Health and Nutrition Examination Survey III, reported that the metabolically normal obese person may be a rarer phenomenon than previously reported and appears to carry an increased risk of all-cause mortality similar to that of the metabolically abnormal obese individual.[19]

OBESITY AND THE METABOLIC SYNDROME

Obesity is identified by measuring WC, rather than body-mass index (BMI), when assessing a patient for the presence of the metabolic syndrome. WC correlates with visceral adiposity and IR and has a stronger association with the development of T2DM and CVD than does BMI.[12,20,21] The 2009 definition of the metabolic syndrome (Table 1) has been updated to include ethnic-specific WC cutoff values to diagnose obesity, as it is now recognized that certain ethnic groups, particularly South Asian populations, have greater amounts of visceral adiposity for given WC measurements compared with European populations.[10,12,22] There is still uncertainty regarding the appropriate cutoff values for diagnosing abdominal obesity in many ethnic groups, due to a lack of sufficient epidemiological data on WC and metabolic risk in many populations.[11,12]

Compared with European populations, certain other ethnic groups, particularly South Asian populations, have greater amounts of visceral adiposity for given measurements of waist circumference.

The World Health Organization identifies two cutoff measurements of WC in men and women, the lower (≥94 cm in men and ≥80 cm in women) being associated with an increased risk of metabolic complications, and the higher (≥102 cm in men and ≥88 cm in women), which correlates with a BMI of ~30 kg/m^2 in men, associated with an even greater risk. The higher cutoff measurements are used by the AHA/NHLBI, Health Canada, and the European cardiovascular societies to identify abdominal obesity in US, Canadian, and European populations, respectively.[12] However, the IDF suggests the lower cutoff should be used in Europoid, Middle Eastern, Mediterranean, and sub-Saharan African populations to define obesity. South Asian populations, Chinese, and Japanese populations, along with Central and South American populations, should be considered obese with a WC of ≥90 cm in men and ≥80 cm in women, according to the IDF.[10] The Chinese Cooperative Task Force, however, applies even lower values, of ≥85 cm in men and ≥80 cm in women.[12] The Japanese Obesity Society is the only society that applies a higher cutoff in women than men (≥85 cm in men and ≥90 cm in women); however, this recommendation is based on one study, the validity of which has been called into question.[12,23,24] Epidemiological data collections in various populations are ongoing to create ethnic-specific criteria for abdominal obesity.

As mentioned, the description of "Syndrome X" in 1988 did not include obesity as part of the syndrome, as Reaven felt IR was the cause of this syndrome, not obesity. Studies investigating the relationship between obesity and IR have shown that although obese individuals are more likely to have IR

Not all obese individuals display the metabolic phenotype associated with increased risk of cardiovascular disease and type 2 diabetes mellitus. Greater degrees of insulin resistance have been associated with higher blood pressure, higher triglyceride levels, low high-density lipoprotein cholesterol, and increased rates of impaired fasting glucose.

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and metabolic syndrome, not all obese individuals display the metabolic phenotype associated with increased risk of CVD and T2DM.[16,17] Greater degrees of IR have been associated with higher blood pressure, higher TG levels, low HDL, and increased rates of impaired fasting glucose.[25,26] Therefore, it appears that it is IR, which is frequently associated with obesity, that leads to the development of the metabolic syndrome.

PREVALENCE

The National Health and Nutrition Examination Survey 2003–2006 reported that 34% of the US population aged >20 years met the modified Adult Treatment Panel III (ATP III) criteria for the metabolic syndrome. These criteria are the same as those outlined in Table 1, except the cutoff for systolic blood pressure was ≥135 mm Hg and abdominal obesity was defined as a WC of ≥102 cm in men and ≥88 cm in women. The prevalence of the metabolic syndrome was similar in men and women, but increased with age and varied by ethnic group. The highest prevalence was found in non-Hispanic white men (37.2%) and Mexican American women (40.6%) (Table 2).[27] Using the ATP III criteria, in European studies the prevalence has been reported to be from 10% to 26%, rates in India have been reported to be from 7.9% to 46% in different populations, the prevalence in Iran has been reported as 24% in men and 42% in women, in Turkey 27% in men and 38.5% in women, and in Filipina American women aged 50–69 years living in the United States, the rate is reported as 34.3%.[28] Rates are lower in Japan, with a prevalence of 8.1% in men and 9.9% in women.[29] In individuals who have T2DM, the prevalence of the metabolic syndrome is reported to be 20%–94%, depending on the population studied.[30,31] The significance of diagnosing the metabolic syndrome in those with T2DM has been questioned, given that all patients with T2DM should have lifestyle and dietary intervention, glycemic control, blood pressure, and lipid management as part of their usual diabetes care and are already identified as having a higher risk of CVD.[31]

According to the National Health and Nutrition Examination Survey 2003–2006, 34% of the US population aged >20 years met the modified National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome.

Depending the population studied, the prevalence of the metabolic syndrome in individuals who have type 2 diabetes mellitus is 20%–94%.

Table 2. *Prevalence of Metabolic Syndrome by Selected Characteristics*[27].

Characteristic	%	OR	95% CI
Sex			
M	35.1	1.0	
F	32.6	0.89	(0.73–1.07)
M			
Age, yr			
20–39	20.3	1.0	
40–59	40.6	2.7	(1.96–3.73)
60+	51.5	4.18	(3.01–5.79)
Race and ethnicity*			
Non-Hispanic white	37.2	1.0	
Non-Hispanic black	25.3	0.54	(0.40–0.73)
Mexican American	33.2	0.78	(0.57–1.07)
BMI*			
Underweight-normal	6.8	1.0	
Overweight	29.8	6.17	(3.96–9.62)
Obese	65	31.92	(20.06–50.78)
F			
Age, yr			
20–39	15.6	1.0	
40–59	37.2	3.2	(2.32–4.43)
60+	54.4	6.44	(4.75–8.72)
Race and ethnicity*			
Non-Hispanic white	31.5	1.0	
Non-Hispanic black	38.8	1.44	(1.05–1.98)
Mexican American	40.6	1.55	(1.06–2.29)
BMI*			
Underweight-normal	9.3	1.0	
Overweight	33.1	5.48	(3.75–8.02)
Obese	56.1	17.14	(12.54–23.44)

Abbreviations: BMI, body-mass index; CI, confidence interval; F, female; M male; OR, odds ratio.
* Race and ethnicity and BMI data are adjusted for age.

PATHOGENESIS

Many factors contribute to the development of the metabolic syndrome. These include lifestyle characteristics such as diet and lack of physical activity, obesity, genetic predisposition, chronic inflammation, and the presence of cytokines, adipokines, elevated free fatty acids (FFAs), mitochondrial dysfunction,

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and alterations in insulin signaling. Uncommon genetic disorders in humans have helped to understand the physiological roles some of these factors play in the metabolic syndrome. Cases of defective insulin activity have been described with rare mutations in the insulin receptor gene (*INSR*) and downstream signaling molecules. The most-severe forms of *INSR* mutations lead to childhood or adolescent death. The less-severe forms cause significant IR, with β-cell compensation and hyperinsulinemia. In later adult life, diabetes may occur in these individuals due to β-cell dysfunction, akin to the development of T2DM following hyperinsulinemia and IR with the metabolic syndrome. Other metabolic abnormalities have not been well characterized in these individuals, as individuals with severe disease die young and less-severe forms may go undiagnosed.[32] However, inherited partial lipodystrophy syndromes have demonstrated the link between IR, visceral adiposity, dyslipidemia, T2DM, and hypertension. Various mutations have been found that lead to partial lipodystrophy syndromes. One of particular interest is the mutation of the gene for peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ is a transcription factor that regulates the transcription of genes concerned with insulin sensitivity, adipocyte differentiation, and inflammation.[32,33] Compared with carriers of other mutations leading to partial lipodystrophy syndromes, carriers of mutations in the PPAR-γ gene have less adipose tissue loss, but more notable hyperinsulinemia and earlier onset of T2DM, with more abnormalities in adipokines and more severe hypertension, suggesting that the IR associated with PPAR-γ gene mutations may be more important than the adipocyte abnormalities in the development of the metabolic syndrome phenotype.[34]

Normal Insulin Action

In an insulin-sensitive individual, glucose stimulates insulin release from the pancreatic β cells. Insulin then decreases plasma glucose concentrations by suppressing hepatic glycogenolysis and gluconeogenesis, as well as by promoting glucose transport into muscle and adipose tissue. Glucose is taken up by muscle and adipose tissue by insulin-responsive glucose transporter 4 (GLUT4), which, under the influence of insulin, is mobilized from intracellular storage vesicles to the cell surface.[35] Exercise increases the expression of GLUT4, and its expression correlates with insulin sensitivity.[36] As well as its effects on glucose uptake, insulin prevents lipolysis in adipose tissue by dephosphorylating and thus inhibiting hormone-sensitive lipase. Hormone-sensitive lipase mediates the hydrolysis of TG in adipocytes with the release of FFAs and glycerol. Glycerol enters the circulation and is taken up by the liver and kidney, where it is converted to glucose by gluconeogenesis.

Insulin activates lipoprotein lipase in adipose tissue, allowing extraction of FFAs from very-low-density lipoprotein (VLDL). These FFAs are used for energy or are re-esterified into TG. In the liver, FFAs are taken up by the liver and processed into VLDL; however, insulin inhibits this process indirectly by decreasing the supply of FFAs to the liver through inhibition of adipose tissue lipogenesis.[37] In addition, insulin suppresses hepatic VLDL synthesis through phosphatidylinositol 3-kinase (PI3K)-mediated suppression of apolipoprotein B (apoB) production.[38] Acutely, insulin appears to inhibit fatty acid synthase, while with chronic hyperinsulinemia, insulin induces fatty-acid synthase activity.[39] In the setting of hyperinsulinemia and IR, there is increased flux of FFAs from adipose tissue to the liver with increased production of VLDL by the liver.[40]

Insulin is transported into the central nervous system (CNS) by insulin transporters in the blood-brain barrier. Low levels of insulin may also be synthesized locally in the brain, although this is the subject of debate.[41] Through insulin receptor signaling in the CNS, insulin decreases appetite.[42] Insulin receptors are found in the olfactory bulb, hypothalamus, hippocampus, amygdale, cerebral cortex, and cerebellum in rodents.[43–45] Binding of insulin to the insulin receptor leads to autophosphorylation of the insulin receptor and activation of signaling pathways, as described below, with phosphorylation of transcription factors that regulate the expression of the genes for neuropeptides, such as neuropeptide Y (NPY), pro-opiomelanocortin (POMC), and Agouti-related protein (AgRP). Insulin suppresses NPY synthesis in neurons of the arcuate nucleus of the hypothalamus, preventing the NPY stimulation of food ingestion. Insulin increases the synthesis of POMC in a second group of neurons of the arcuate nucleus. POMC is cleaved to form α-melanocyte stimulating hormone (α-MSH), which acts on melanocortin 3 receptors and melanocortin 4 receptors to decrease food intake.[46] Insulin signaling activates the adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels in the arcuate nucleus, decreases AgRP release, and through the vagus nerve, leads to decreased glucose production by the liver by decreasing gluconeogenic enzymes (phosphoenolpyruvate carboxykinase, glucose 6-phosphatase).[47,48] Additionally, CNS insulin signaling has been shown to increase adipose tissue

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lipoprotein lipase activity, adipose tissue mass, and adipocyte size.[49] In insulin-resistant states, there appears to be a decrease in cerebrospinal fluid insulin relative to serum insulin levels, leading to a relative CNS insulin deficit.[50] This is thought to be related to a decreased sensitivity of the insulin receptors in the blood-brain barrier to circulating insulin, in addition to resistance of the CNS structures to the action of insulin.[47,51,–53]

Normal Insulin Signaling

Insulin can exert metabolic and mitogenic effects on cells through its binding to the insulin receptors and subsequent activation of signal transduction pathways. Insulin binding to the insulin receptors results in its autophosphorylation at sites on the intracellular β subunit. Autophosphorylation of the insulin receptors leads to the activation of tyrosine kinases and phosphorylation of other proteins. These proteins include insulin receptor substrates (IRS) and certain adaptor proteins that then act as docking sites for the phosphorylation of downstream effectors.[54] The pathways through which insulin mediates its metabolic activity are initiated by PI3K and the oncogene Cbl and its associated protein (CAP). Insulin transmits its growth effects through its action on the mitogen-activated protein kinase (MAPK) pathway.[55] Activation of the PI3K pathway ultimately leads to the activation of the protein kinase Akt and the phosphorylation of transcription factors, such as the FOXO1 member of the forkhead family of transcription factors. Phosphorylation of these transcription factors prevents their entry into the cell nucleus, thereby inhibiting their action. The FOXO1 transcription factor regulates the genes for hepatic gluconeogenesis; therefore insulin signaling decreases transcription of gluconeogenic genes.[56] FOXO1 also interacts with the promoter of another transcription factor, PPARγ. PPARγ regulates the GLUT4 gene transcription, FOXO1 inhibits the expression of PPARγ, whereas insulin signaling releases the suppression by FOXO1.[57] Signaling through a second pathway involves phosphorylation of the Cbl/CAP pathway and leads to actin-mediated mobilization of Glut4 to the cell surface, allowing for increased glucose uptake.[58] Activation of the MAPK pathway leads to phosphorylation of transcription factors involved in cell growth. These pathways interact with each other and are also regulated by other factors that may inhibit insulin signaling and contribute to IR. The elements involved in IR are outlined in Figure 1.

Factors Involved in Insulin Resistance

Free Fatty Acids

Human studies in nondiabetic, nonobese volunteers have shown that infusing lipid emulsions can cause IR and impaired glucose uptake in skeletal muscle.[59] Further, high FFA levels decrease Glut4 levels in human cardiac muscle.[60] Lowering FFA levels in obese nondiabetic individuals led to normalization of insulin-mediated glucose uptake by skeletal muscle. In individuals with obesity and T2DM, when FFA levels were lowered, insulin sensitivity improved.[61]

FFAs are absorbed from the intestine into the circulation in the form of chylomicrons. They also enter the circulation after lipolysis of adipose tissue. In obese individuals, FFAs are increased, despite elevated levels of insulin. This is thought to be due to increased adipose tissue lipolysis from a reduction in insulin's usual inhibition of hormone-sensitive lipase. The increase in FFAs then further impairs insulin signaling, leading to a greater increase in circulating FFA levels. In addition, there is reduced lipogenesis in the adipocytes due to decreased activity of transcription factors such as PPARγ.[62] As FFA levels increase, uptake into adipose tissue exceeds its oxidation and so metabolites involved in esterification accumulate. These include long-chain acyl coenzyme A (acyl CoA) and diacylglycerol (DAG). DAG also disrupts normal insulin signaling by serine phosphorylation of IRS, through activation of protein kinase C. Serine phosphorylation prevents tyrosine phosphorylation and thus impairs insulin signaling. Ceramide is another lipid molecule that accumulates in skeletal muscle of obese individuals. It activates the enzyme protein phosphatase 2A, leading to dephosphorylation of Akt, thereby blocking insulin signaling and inhibiting Glut4 translocation to the cell membrane, thus disrupting insulin-mediated glucose uptake into skeletal muscle.[63]

In the liver, FFAs inhibit the insulin-induced suppression of glycogenolysis and gluconeogenesis.[64] In

Free fatty acids inhibit the insulin-induced suppression of glycogenolysis and gluconeogenesis.

animal studies, consuming a high-fat diet caused increased levels of FFAs and resulted in the loss of suppression of hepatic gluconeogenesis.[65] The increased supply of FFAs to the liver from adipocyte lipolysis enables the hepatic production and release of VLDL. Adipocytes also produce increased amounts of cholesterol ester transferase protein that decreases

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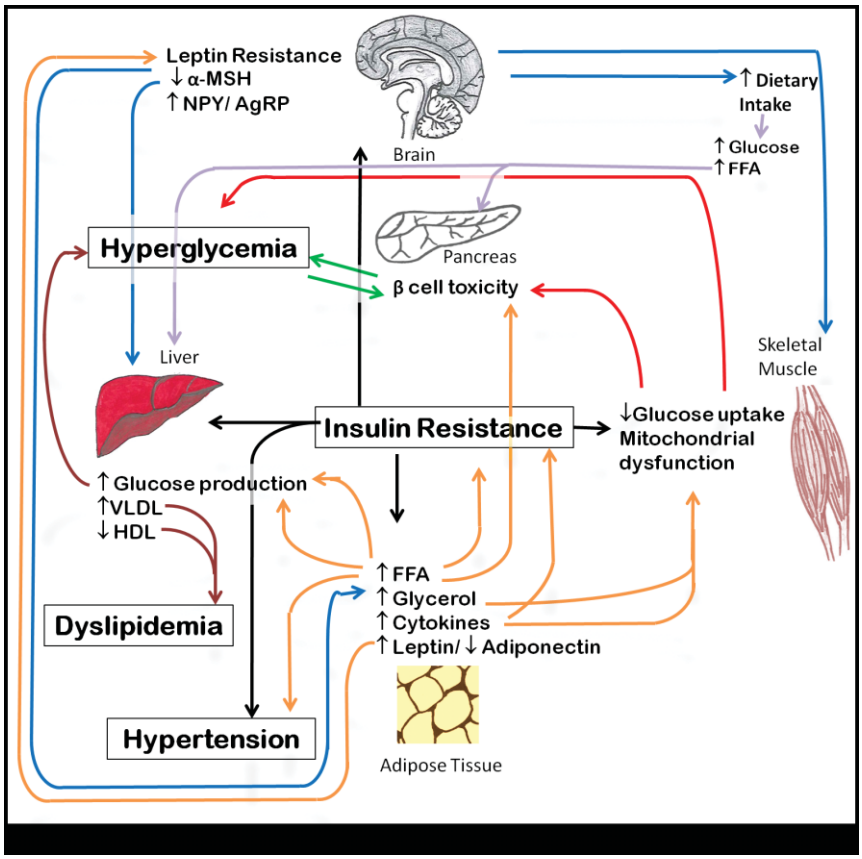

Fig 1. Insulin resistance in the development of the metabolic syndrome. Adipose tissue: leptin production increases due to leptin resistance, along with increased production of cytokines, diacyglycerol, and FFAs. Adiponectin levels decrease with increasing obesity. Adipose tissue production of cytokines, acyl Co A, diacylglycerol, and FFAs leads to insulin resistance, mitochondrial dysfunction, dyslipidemia, decreased glucose uptake by skeletal muscle, increased glucose production by the liver, and β-cell toxicity. Hyperglycemia ensues. The hyperglycemia can in turn cause further β-cell toxicity. Insulin resistance also leads to hypertension through its actions on the nitric oxide and endothelin-1 in the endothelium. Decreased insulin signaling in the brain results in increased dietary intake, as well as loss of suppression of hepatic gluconeogenesis and increased production of lipogenesis intermediated by adipose tissue. **Abbreviations:** acyl CoA, long-chain acyl coenzyme A; AgRP, Agouti-related protein; α-MSH, α-melanocyte stimulating hormone; FFA, free fatty acids; HDL, high-density lipoprotein cholesterol; NPY, neuropeptide Y; VLDL, very-low-density lipoprotein cholesterol.

HDL levels by facilitating the transfer of cholesteryl esters from HDL to VLDL.[66] This contributes to low HDL and increased TG levels. In addition, increased hepatic lipase degrades HDL and the liver exchanges VLDL for HDL.[67] Finally, there is evidence that the HDL level in insulin-resistant individuals with and without hypertriglyceridemia is largely determined by the fractional catabolic rate of apolipoprotein A-I and A-II (the major lipoproteins that constitute HDL). It has been suggested that individuals with low HDL levels, such as those with the metabolic syndrome, have more loosely bound apoA-1 that is more readily catabolized by the kidneys.[68,69]

FFAs also contribute to the development of non-alcoholic fatty liver disease in insulin-resistant individuals. When FFAs are released from visceral adipose tissue into the portal circulation and from subcutaneous adipose tissue into the peripheral circulation, they may be taken up by hepatocytes and bound to CoA. Fatty acyl CoA can then form hepatic TG or interfere with insulin signaling and induce inflammation in hepatocytes. In insulin-resistant states, insulin can activate the transcription factor SREBP-1, increasing the transcription of genes involved in hepatic lipogenesis. Glucose activates another transcription factor, carbohydrate response element binding

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protein (ChREBP). ChREBP stimulates the glycolysis of glucose into pyruvate, which forms acetyl CoA and subsequently malonyl CoA, which is involved in FFA synthesis. Both ChREBP and SREBP transcription factors are increased in animal models of fatty liver. Additionally, de novo lipogenesis is increased, possibly through activation of the transcription factor FOXA2. In mouse studies, IR is associated with impaired Foxo1 signaling, but Foxa2 phosphorylation is preserved. Together, these alterations in glucose and lipid metabolism can lead to hepatic lipogenesis and the development of nonalcoholic fatty liver disease.[62,70,71]

Inflammatory Cytokines

FFAs also increase inflammation by signaling through the receptor that normally interacts with the lipopolysaccharide membrane of gram-negative bacteria (Toll-like receptor 4). This interaction causes activation of the nuclear factor κB transcription factor and increased synthesis of cytokines and chemokines, including tumor necrosis factor α (TNFα); interleukins (IL) IL-1 β and IL-6; and monocyte chemoattractant protein-1 (MCP-1). This leads to a state of chronic inflammation in obese individuals.

The inflammatory cytokines IL-6 and TNFα are produced by adipose tissue macrophages. Cytokines can interfere with insulin action by serine phosphorylation of IRS and prevent downstream signaling through the PI3K pathway.[72] They trigger the production of proinflammatory cytokines that also cause serine phosphorylation of IRS and impair insulin signaling. These proinflammatory cytokines up-regulate proinflammatory genes and thus propagate the inflammatory signaling. TNFα also decreases endothelial nitric oxide synthase (eNOS), leading to decreased expression of mitochondrial oxidative phosphorylation genes, increasing oxidative cellular stress and the accumulation of reactive oxygen species (ROS).

Mitochondrial Dysfunction

In the cell, the mitochondria are involved in energy production in the form of ATP, through oxidative phosphorylation and the transfer of electrons through the respiratory chain. There is a link between mitochondrial dysfunction and IR, before the development of obesity and T2DM. Insulin-resistant, physically inactive, obese individuals and those with T2DM have smaller and fewer mitochondria in skeletal muscle. In addition, studies in humans have shown a down-regulation of genes involved in mitochondrial oxidative phosphorylation. Therefore, insulin-resistant individuals may have a lower number of mitochondria, with impaired function. The exact mechanisms by which IR leads to mitochondrial dysfunction are unclear, but there appears to be decreased expression of the transcription factor coregulator of nuclear receptors coactivator 1α (PGC-1α) in insulin-resistant individuals.[73,74]

Mitochondrial dysfunction leads to decreased lipid oxidation, with the accumulation of lipid metabolites DAG, ceramide, and acyl CoA. These in turn cause impaired insulin signaling, as described. It also leads to increased oxidative stress and increased ROS formation, and a vicious cycle ensues as these elements contribute to further mitochondrial dysfunction. Impairment of mitochondrial activity may lead to decreased ATP formation and the perception of an energy deficit by the brain, causing appetite stimulation.[73]

The production of ATP by the mitochondria is driven by a proton gradient across the inner mitochondrial membrane. Mitochondria may generate heat by the "proton leak" as protons leak from the intermembrane space across the inner mitochondrial membrane into the matrix. There are 3 uncoupling protein that play a major role in this process. Mitochondrial uncoupling results in elevation of long-chain acyl CoA and the formation of DAG, which in turn activates protein kinase C, which interferes with normal insulin signaling.[75]

Adipokines

Leptin is a protein produced by adipocytes that controls appetite and energy expenditure. Absence of leptin leads to extreme obesity and IR. However, most obese individuals do not have a leptin deficiency; instead, they have increased levels of leptin, but are resistant to its appetite-suppressing effects.[76] Elevated TG levels decrease leptin transport into the CNS, which, along with impaired leptin signaling, may lead to leptin resistance.[44,48] The leptin receptors are mostly located in the brain, adipocytes, and endothelial cells. Many of the metabolic effects of leptin are via the hypothalamus, through its regulation of NPY and α-MSH, in a manner similar to insulin.[48,76] Animal studies have shown that leptin promotes lipid oxidation and protein synthesis. In studies on rat adipocytes, leptin reduces insulin's lipogenic effects, potentially due to its inhibition of insulin binding to the adipocyte.[77] Leptin also depletes triglyceride content of adipose tissue without increasing circulating FFAs, due to increased mitochondrial oxidation. In this way it also opposes the actions of insulin.[76–78] Leptin

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does not seem to interfere with insulin actions on glycogen synthesis or glycolysis. As well as its effects on lipid, protein, and glucose metabolism, leptin also stimulates T-cell proliferation, increases the production of inflammatory cytokines, and regulates the reproductive system.[79] Leptin resistance leads to loss of leptin's appetite suppression and increased adiposity.

Adiponectin is another protein produced by adipocytes. It has anti-inflammatory and antiatherogenic properties and regulates food intake.[80–83] Adiponectin levels are absent in mice without adipose tissue; however, IR and increased intra-abdominal fat is also associated with decreased levels of adiponectin.[84,85] Binding of adiponectin to its receptors (AdipoR1 and AdipoR2) leads to the activation of several signaling pathways involved in the regulation of glucose, protein, and fatty-acid metabolism. Phosphorylation of AMP-activated protein kinase (AMPK) as a result of adiponectin signaling leads to increased glucose uptake in the muscle and decreased hepatic gluconeogenesis. Adiponectin deficiency is also linked to increased atherogenesis, elevated levels of small dense LDL and TG levels, along with increased inflammatory cytokines.[77,85] The exact mechanisms through which IR leads to low adiponectin levels and the involvement of adiponectin in the development of the metabolic syndrome remain unclear.[86]

Resistin is another adipokine that is increased in animal models of obesity. It has been shown to lead to impaired insulin action and glucose intolerance. It appears to cause β-cell apoptosis in rat insulinoma cells and so has been postulated to lead to β-cell dysfunction in T2DM.[87] In addition, resistin activates the suppressor of cytokine signaling proteins that inhibit phosphorylation of the insulin receptor and downstream insulin signaling proteins, thus leading to impaired insulin signaling.[88] It also impairs glucose uptake by skeletal muscle and the liver and increases hepatic gluconeogenesis.[89,90] Other adipokines that have been identified include apelin, visfatin, and retinol binding protein-4. Some studies have found positive correlations between these adipokines and IR, although their exact roles and mechanisms remain to be determined.[91]

METABOLIC EFFECTS OF INSULIN RESISTANCE

Together, abnormalities in insulin sensitivity, FFA levels, cytokine production, mitochondrial function, and levels of adipokines contribute to the development of hypertension, dyslipidemia, and hyperglycemia and comprise the metabolic syndrome (Figure 1).

Abnormalities in insulin sensitivity, free fatty acid levels, cytokine production, mitochondrial function, and levels of adipokines contribute to the development of hypertension, dyslipidemia, and hyperglycemia and comprise the metabolic syndrome.

Hypertension and Insulin Resistance

Hypertension is present in 15% of males and females with a BMI of $\leq$25 kg/m^2 and increases to 42% of males and 38% of females with a BMI of $>$30 kg/m^2.[92,93] Studies have shown that IR or hyperinsulinemia is present in the majority of hypertensive patients, suggesting a link between obesity, glucose intolerance, and hypertension. Insulin is a stimulator of the vasodilator nitric oxide (NO) through insulin-mediated PI3K signaling and phosphorylation of eNOS. Under normal circumstances, vasodilatation occurs in the skeletal-muscle vasculature in response to insulin release after eating and promotes glucose disposal.[94] In opposition to NO, endothelin-1 (ET-1) is a potent vasoconstrictor, which is stimulated by insulin activity through the MAPK pathway. NO is an inhibitor of ET-1. However, it has been proposed that in insulin-resistant states, insulin signaling through the PI3K pathway is impaired, leading to decreased NO. In addition, increased cytokines, such as IL-6, along with low adiponectin levels and leptin resistance, cause decreased NO and increased action of ET-1, with the subsequent development of hypertension. FFA can also induce hypertension by increased production of ROS, which increase oxidative stress and decrease NO.[93,94] Hyperinsulinemia may also lead to increased peripheral vascular resistance due to sympathetic overactivity, volume expansion from its antinatriuretic effects, and increased antiotensinogen II.

Dyslipidemia and Insulin Resistance

The dyslipidemic profile of the metabolic syndrome involves low HDL and elevated TG. In a meta-analysis of prospective studies, it was reported that those with TG levels in the top third of the population had a relative risk of coronary disease of 1.7 (95% confidence interval: 1.6–1.9) compared with those with TG levels in the bottom third.[95] The onset of IR

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has a profound effect on lipid profiles.[96] IR results in the increased production of FFA from adipocytes through loss of its inhibition of hormone-sensitive lipase. Additionally, endothelial lipoprotein lipase function is impaired, both events leading to the increase in circulating FFAs. The increased influx of FFAs to the liver, and insulin stimulation of hepatic lipogenesis, lead to increased hepatic TG production in the form of VLDL and steatosis as the TG are stored in the liver.[35,67] Adipocyte production of cholesterol ester transferase protein allows for the transfer of cholesteryl esters from HDL to VLDL. There is increased clearance of HDL by the kidneys and the liver takes up HDL and produces VLDL, therefore leading to the low HDL and elevated TG levels seen with the metabolic syndrome.[66,67,69]

The increased influx of FFAs to the liver, and insulin stimulation of hepatic lipogenesis, lead to increased hepatic triglyceride production in the form of very-low-density lipoprotein and steatosis as the triglycerides are stored in the liver.

Hyperglycemia and Insulin Resistance

IR is a key element in the development of hyperglycemia and T2DM. In normal individuals, ingestion of nutrients results in the secretion of insulin from the pancreatic β cells. Specific triggers for insulin release include glucose, amino acids, FFAs, and gastrointestinal hormones, such as glucagon like peptide-1. There is a rapid first-phase insulin response that occurs immediately after eating, peaks at 10 minutes, and disappears after approximately 20 minutes. Its effect is to inhibit hepatic glucose production and promote glucose uptake. This is followed by a second-phase insulin response, which begins at 15–20 minutes and peaks during the next 20–40 minutes.[97]

In IR and T2DM, the initial β cell abnormality is loss of the first-phase insulin response, followed by an exaggerated second-phase response. This ultimately leads to hyperinsulinemia. Chronic nutrient overload leads to β-cell toxicity and eventually β-cell failure.

This can be seen in animal models, where chronic hyperglycemia leads to increased basal insulin levels, but loss of β-cell response to glucose stimulation. In the presence of hyperglycemia, FFAs can also cause β-cell dysfunction, by inducing enzymes of β-oxidation, leading to increased acetyl CoA levels, activation of pyruvate carboxylase and pyruvate cycling in the islet cells. This also causes elevated basal insulin levels and impaired glucose stimulated insulin release. The toxic effects of glucose and lipids are also seen in human β cells, and are referred to as glucotoxicity and lipotoxicity, respectively.[98,99]

Chronic nutrient overload leads to β-cell toxicity and eventually β-cell failure. Human β cells also show the toxic effects of glucose and lipids, which are referred to as glucotoxicity and lipotoxicity, respectively.

Increased demand for insulin leads to endoplasmic reticulum stress and cell death. Amylin, which is hypersecreted with insulin from the β cell, can form amyloid fibrils that can accumulate in β-cells and also induce β-cell dysfunction. In normal circumstances, in insulin-sensitive individuals, there is a feedback loop between the β cells and the liver, skeletal muscle, and adipose tissue. To maintain euglycemia, the β cells have to increase or decrease secretion in response to signals from these tissues. Failure of the feedback loop leads to the development of impaired glucose tolerance and T2DM.[98,99]

CONCLUSION

The presence of the metabolic syndrome should be considered in the evaluation of overweight and obese patients, as it may identify those at greatest risk of developing T2DM and CVD in the future. The diagnostic criteria have now been harmonized and simplified from the previous versions to provide a practical and useful set of criteria that can be used in the physician's office and allows agreement for comparison amongst epidemiological studies. Although the diagnosis may be less complicated, the mechanisms by which the metabolic syndrome develops are the subject of ongoing research and are becoming more complex, with interplay between insulin signaling, inflammation, mitochondrial function, adipokines, FFAs, lipid production, glucose uptake, genetics, lifestyle, and diet. While obesity may exaggerate the

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metabolic syndrome phenotype, it appears that IR is the key element that can be present in both obese and lean individuals and leads to the derangements in lipids, blood pressure, and glycemic control that characterize the metabolic syndrome.

DISCLOSURES

Potential conflict of interest: Nothing to report.

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