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VASCULAR BIOLOGY OF METABOLIC SYNDROME

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INTRODUCTION

The metabolic syndrome is a constellation of risk factors of metabolic origin that are accompanied by increased risk for cardiovascular disease and type 2 diabetes mellitus. Insulin resistance, which results in this risk-factor clustering, may contribute to many of the untoward outcomes attributed to the metabolic syndrome (1). The clinical risk factors are atherogenic dyslipidemia (low high density lipoprotein and high triglycerides levels), elevated blood pressure, elevated plasma glucose, a prothrombotic state, and a pro-inflammatory state (Figure 1). Metabolic syndrome is also characterized by hyperinsulinemia, low glucose tolerance and truncal obesity. Lipid profile abnormalities, such as elevated serum triglyceride levels and reduced high density lipoproteins, have been found in the majority of studies of intermittent claudication (2) and there is a strong inverse relationship between high-density lipoprotein levels and claudication severity (3). It has been estimated that 50% of diabetic patients have evidence of peripheral artery disease (PAD) (4). However, a study of 100 consecutive 'non-diabetic' patients attending a vascular clinic showed abnormal glucose tolerance tests in 40% (5). This was despite all 40 patients having normal random or fasting blood glucose levels. Two definitions of metabolic syndrome predominate in the literature, the National Cholesterol Education Program (NCEP) and the World Health Organization (WHO) (Table 1). Metabolic syndrome is defined as the presence of 3 or more of the following: (1) waist circumference ≥88 cm in women and ≥102 cm in men; (2) fasting triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides; (3) HDL-cholesterol <50 mg/dL in women and <40 mg/dL in men or drug treatment for reduced HDL-cholesterol; (4) BP ≥130/85 mm Hg or use of BP-lowering medication; and (5) fasting glucose ≥100 mg/dL or use of glucose-lowering medication (6). If waist circumference is not available, a body mass index (BMI) >30 kg/m^2 can be used as a determinant for abdominal obesity (7). The prevalence of metabolic syndrome in the adult

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population in developing countries is 22–39% and varies depending on the definition used and on ethnicity (8–10). Using either WHO or NCEP definitions (Table 1) metabolic syndrome is associated with future coronary heart disease events and type 2 diabetes. Both definitions will predict cardiovascular mortality, while the NCEP definition can predict all cause mortality. While the age-dependent prevalence of the metabolic syndrome is between 20% and 40% in healthy subjects (11), metabolic syndrome is present in approximately 45% of patients with symptomatic peripheral vascular disease and is higher in those with lower extremity atherosclerotic occlusive disease (prevalences of 52% to 58%) (12,13).

OBESITY, ADIPOCYTES, LIPIDS AND ADIPOKINES

Obesity/Adipose Tissue

In humans, two types of adipose tissue have been defined which are considered to have essentially antagonistic functions: white adipose tissue (WAT) stores excess energy as triglycerides and brown adipose tissue (BAT) is responsible for the dissipation of energy through the production of heat. BAT is abundant in small mammals and in newborns and helps them to survive cold temperatures (14). Recent investigations, however, have shown that adults also have metabolically active BAT and that BAT may play an important role in energy homeostasis. WAT stores energy in the form of triglycerides and accumulated WAT is the adipose tissue responsible for metabolic syndrome.

Adipose tissue is a heterogeneous mix of adipocytes, stromal pre-adipocytes, immune cells, and endothelium (15). Adipose tissue develops in several distinct anatomical depots within the body, and the differential expansion of these depots is of great importance. Expansion of visceral or abdominal white adipose tissue has been most strongly correlated to insulin resistance and cardiovascular disease in humans and animals (16). Conversely, expansion of subcutaneous WAT does not appear to have the same negative systemic consequences on metabolism (17). Adipose tissue possesses a relatively dense network of blood capillaries, ensuring adequate exposure to nutrients and oxygen. WAT varies in its vascularity, both between depots and within the tissue itself (18). The balance between angiogenesis and hypoxia has a significant impact on the modulation of “good” versus “bad” tissue expansion, thereby implicating the local microvasculature as a key modulator of the systemic impact adipose depots (17,19,20).

The adipose tissue of obese humans contains increased numbers of macrophages, and once activated, these macrophages secrete a range of cytokines such as TNF-α, IL-6, and IL-1 (21). The adipose tissue resident macrophages are responsible for the expression of most of the tissue’s TNF-α and IL-6. The expression of macrophage markers in human adipose tissue is high in subjects with obesity and insulin resistance, and can be correlated with the expression of TNF-α and IL-6 (22,23). Adipocytes express low levels of monocyte chemoattractant protein (MCP)-1, and increased expression is found in obese subjects (23). Recent studies suggest that macrophages infiltrate adipose tissue as part of a scavenger function in response to adipocyte necrosis. Immunohistological studies of human adipose tissue have demonstrated that most of the macrophages in adipose tissue are surrounding dead adipocytes and form a syncytium, often referred to as a “crown-like structure” (24), and the macrophage burden surrounding necrotic adipocytes increases significantly (25). The adipocyte secretes several factors that modulate the production of new blood vessels (e.g., angiopoietin-1, angiopoietin-2, vascular endothelial growth factor (VEGF), transforming growth factor β (TGF-β), hepatic growth factor (HGF), stromal derived factor 1 (SDF-1), TNF-α, resistin, leptin, tissue factor, placental growth factor (PGF), and insulin-like growth factors (IGF)) (26). There is evidence suggesting that the vascular network forms before the mature lipid-carrying adipocytes reside in the area, thus providing access of secreted cytokines and adipokines to the circulation (27). Despite this great angiogenic

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potential, the rapidly expanding fat pad still experiences hypoxia and necrosis (28,29). The induction of adipocyte hypoxia *in vitro* results in the expression of a number of inflammatory cytokines (30–32). The adipose tissue expandability hypothesis states that a failure in the capacity for adipose tissue expansion, rather than obesity per se is the key factor linking positive energy balance and type 2 diabetes. Each individual possesses a maximum capacity for adipose expansion, which is determined by both genetic and environmental factors. Once the limit of adipose tissue expansion is reached, adipose tissue ceases to store energy efficiently and lipids begin to accumulate in other tissues. Ectopic lipid accumulation in non-adipocyte cells induces insulin resistance, apoptosis and inflammation (33). Adipocytes are potent sources of such adipokines, which mediate many parts of the biology encountered. There are two types of adipocytokines: adipose-tissue-specific bioactive substances (true adipokines) and adipokines that are abundantly secreted from adipose tissue, but which are not specific for adipose tissue.

Lipoprotein Metabolism

Obesity, an increased mass of activated adipocytes and their linked changes in lipoproteins, is a major component in the biology of metabolic syndrome. Chronic inflammation associated with visceral obesity induces altered lipoprotein metabolism and insulin resistance in the liver (34). Abnormalities in the transport of lipoprotein diminish the catabolism of the very low density lipoprotein (VLDL) and increase the catabolism of the high density lipoprotein (HDL), which creates insulin resistance. This process is associated with a lower concentration of the adipokine, adiponectin (*vide infra*) that in turn regulates the catabolism of VLDL and HDL, consequently increasing the flow of fatty acids from the adipose tissue to the liver and muscles (35). Accumulation of lipid metabolites within non-adipose tissues can induce chronic inflammation by promoting macrophage infiltration and activation and tissue damage. Oxidized and glycated lipoproteins, free fatty acids (FFA), free cholesterol, triacylglycerols, diacylglycerols and ceramides induce cellular dysfunction through their pro-inflammatory and pro-apoptotic properties (36). Emerging evidence also suggests that macrophage activation by lipid metabolites and further modulation by lipid signaling, represents a common pathogenic mechanism underlying lipotoxicity in atherosclerosis, obesity-associated insulin resistance, liver steatosis and chronic kidney disease. Lipid derivatives, through modulation of macrophage function, promote plaque instability in the arterial wall, impair insulin responsiveness and contribute to inflammatory liver, muscle and kidney disease (36). In metabolic syndrome, the regulation of fat storage and energy supply by adipose tissue is impaired leading to elevated plasma FFA levels, excessive metabolism of FFAs, and high levels of FFA metabolites in non-adipose tissue (37). FFAs and their metabolites act as metabolic mediators of insulin resistance. It has been proposed that insulin resistance occurs in adipose tissue before muscle insulin resistance (38). In adipose tissue, insulin resistance of obesity is characterized by an inadequate insulin action in the fed state that resembles conditions in the normal fasting state. This results in the release of FFAs into the circulation to deliver energy to skeletal muscle. Thus, postprandial FFAs are directly transported to the skeletal muscle and liver, where energy is not needed. FFAs and their metabolites also act as signaling molecules interacting with insulin signaling (39) and have direct effects on glucose transport (37,40,41). Reducing ectopic fat in the skeletal muscle of diabetic patients might therefore be a promising target for diabetes therapy and might partly explain the action of the diabetic drug, thiazolidinedione (42).

Adipokines

Adipocytes secrete a variety of hormones, cytokines, growth factors and other bioactive substances, conceptualized as adipocytokines, including plasminogen activator inhibitor 1 (PAI-1), tumor necrosis factor (TNF-α), leptin and adiponectin (Table 2) (43). Dysregulated

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production of these adipocytokines is part of the pathogenesis of metabolic syndrome (Figure 2). Increased productions of PAI-1 and TNF-α from accumulated fat contribute to the formation of thrombosis and insulin resistance in obesity, respectively. A lack of leptin causes metabolic syndrome. Adiponectin exerts insulin-sensitizing and anti-atherogenic effects, hence decrease of plasma adiponectin is causative for insulin resistance and atherosclerosis in obesity (44).

Leptin

Leptin is a 167-amino acid hormone secreted largely by adipose tissue that controls food intake and energy expenditure (45). Circulating levels of leptin parallel fat cell stores, increasing with overfeeding and decreasing with starvation. While the absence of leptin or a mutation in leptin receptor genes induces a massive hyperphagia and obesity in humans (46,47), the prevalence of these mutations in obese humans is rare. The effects of leptin are mediated by receptors, mainly located in the central nervous system, and in other tissues, including adipocytes and endothelial cells. Leptin receptor belongs to the class I family of cytokine receptors, and it engages both the signal transducer and activator of transcription-3 (STAT3) pathway and the insulin receptor substrate phosphoinositide-3 kinase pathway (48). It has been shown that STAT3 is essential for mediating food intake, liver glucose production, and gonadotropin secretion (48); however, the control of adipose tissue metabolism by leptin is STAT3 independent (49). Infusion of leptin into the hypothalamus led to the suppression of lipogenesis in adipose tissue through activation of the phosphoinositide-3 kinase pathway, the sympathetic nervous system, and the engagement of the adipose tissue endocannabinoid system (49). Leptin modulates the T-cell immune response, stimulates proliferation of T-helper cells, and increases production of pro-inflammatory cytokines by regulating different immune cells (50,51).

Adiponectin

Adiponectin is a 30-kDa protein secreted from adipocytes (52). Circulating adiponectin is found in several different isoforms: trimer, low-molecular weight (hexamers), and high-molecular weight (HMW) (18mers) forms (53,54), each with distinct biological functions (55). The HMW isoform is linked to the insulin-sensitizing effects of adiponectin, while the central effects of adiponectin are linked to the hexamer and trimer isoforms (56). Adiponectin is present in cerebrospinal fluid largely in the trimer and hexamer forms (57). Adiponectin increases food intake by enhancing hypothalamic AMPK activity in fasting conditions (58). Circulating levels of adiponectin are decreased in obesity-induced insulin resistance (59,60). The HMW oligomer of adiponectin is inversely associated with the risk for diabetes independent of total adiponectin levels (61), and is responsible for the association of adiponectin with traits of metabolic syndrome (62,63). Adiponectin binds two transmembrane receptors (AdipoR1 and AdipoR2) that are ubiquitously expressed. AdipoR1 is predominantly expressed in skeletal muscle with a preference for binding to globular adiponectin, whereas AdipoR2 is most abundant in the liver with a preference for binding to full-length adiponectin (64). Adiponectin improves insulin sensitivity by increasing energy expenditure and fatty acids and by the expansion of subcutaneous adipose tissue with decreased levels of macrophage infiltration (65), similar to the actions of PPARγ agonists. Thiazolidinediones are known to increase circulating levels of adiponectin, mostly the HMW form, by 2- to 3-fold (66–68), and improve insulin resistance by diversion of fat from ectopic sites to subcutaneous adipose tissue (69). Interestingly, the insulin-sensitizing effects of Thiazolidinediones are significantly diminished in the absence of adiponectin (70), suggesting an important role of adiponectin in reduction of the lipotoxicity and inflammation associated with obesity. Adiponectin has also had vasculoprotective effects through an increase in endothelial nitric oxide (NO) production and modulation of expression of adhesion molecules and scavenger receptors (71,72).

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Resistin

Resistin is a 12-kDa peptide that is part of a gene family of "Resistin-like molecules," produced by resistin (73). Resistin is expressed by adipocytes in mice but is expressed by the macrophages of humans (74). Resistin is a 12 kDa protein that circulates as either a trimer (monomeric form of the peptide hormone) or hexamer (dimeric form of resistin). The monomeric form was shown to impair hepatic insulin action more potently than the dimerized form (75). In contrast, the dimerized form of resistin was shown to be more effective in antagonizing insulin-stimulated glucose uptake in adult murine cardiomyocytes (75). A number of studies have examined plasma resistin levels or adipose resistin expression, and have found variable associations with insulin resistance (76–79). High plasma levels of resistin correlate with proatherogenic inflammatory markers, metabolic syndrome, increased cardiovascular risk, unstable angina, and poor prognosis in coronary artery disease. Resistin increases pro-inflammatory markers and induces the release of endothelin 1 and the production of vascular cell adhesion molecule 1 and MCP-1. A recent large study involving the Framingham offspring cohort found a significant relationship between insulin resistance and resistin; however, this relationship was considerably weaker than the relationship with adiponectin, and was lost after adjustment for BMI (80). Resistin decreases after Thiazolidinediones treatment of humans, although resistin was also decreased by metformin treatment (66,81).

Retinol binding protein 4

Retinol binding protein 4 (RBP4) is a highly-expressed circulating adipokine that can lead to insulin resistance. Many studies have demonstrated a positive association between RBP4 and insulin resistance or obesity, whereas others have not found such a relationship. There are suggestions of an age-related difference with younger people demonstrating the relation while older persons do not (82). RBP4 is associated with adipose tissue macrophage markers, suggesting a link between RBP4 and inflammation within adipose tissue (83). RBP4 circulates bound to transthyretin, which decreases RBP4 renal clearance, and transthyretin plasma levels are increased 4-fold in murine models of metabolic syndrome (84). There is an association of RBP4 and Glut4, which is presumed to play a role in fuel sensing in the adipocyte.

Visfatin

Visfatin is expressed in many cells and tissues, and was previously identified as a protein involved in B-cell maturation (pre-B colony enhancing factor) (85,86). Visfatin has insulin-like functions, and is predominantly found in visceral adipose tissue (87). In human studies, a positive correlation between visceral adipose tissue visfatin gene expression and BMI was noted, along with a negative correlation between BMI and subcutaneous fat visfatin (88,89), suggesting that visfatin regulation in these different depots is different, and adipose depot ratios are highly dependent on the obesity of the subjects. No difference in visfatin expression between fat depots of humans was noted (88,89), and visfatin was expressed predominantly by non-macrophage cells in the adipose tissue stroma (89). Plasma visfatin can be positively associated with BMI (88). Visfatin can up-regulate IL-6 and TNF-α *in vivo* and *in vitro* (75). Visfatin can increase matrix metalloproteinase-9 (MMP-9) activity in monocytes, and TNF-α and IL-8 in peripheral blood mononuclear cells (90).

Tissue Inhibitor of Metalloprotease-1 (TIMP-1)

TIMP-1 is another new candidate adipokine. TIMP-1 is the constitutive inhibitor for the gelatinase MMP-9. The expression and secretion of TIMP-1 are upregulated by pro-inflammatory cytokines in obese patients and *in vitro* so it is possible that TIMP-1 has a role in maintaining adipose tissue mass in obesity (91,92).

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Heparin-binding epidermal-growth-factor-like growth factor

Heparin-binding growth factors are a family of mitogenic proteins that have varying affinities for heparin and heparin-like molecules. They include platelet-derived growth factor (PDGF), acidic fibroblast growth factor (aFGF), basic FGF (bFGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and heparin-binding epidermal growth factor (HBEGF). HBEGF is expressed in adipocytes and its plasma levels increase with the extent of obesity. HBEGF is a 22-kDa growth factor that is mitogenic for fibroblasts and smooth muscle cells. It acts by binding to the EGF receptor and, in fact, has a greater affinity for EGF receptors on smooth muscle cells and is a more potent mitogen for smooth muscle cells than EGF itself.

Angiotensinogen

The angiotensinogen gene is detected in adipose tissue, although mRNA expression is not correlated with adiposity. Angiotensinogen is the precursor of angiotensin-I which, after conversion to angiotensin-II, plays a major role in blood pressure regulation. Angiotensinogen mRNA expression is increased in visceral fat (93,94), which partially explains the relationship between systemic hypertension and obesity in the metabolic syndrome. Angiotensinogen knockout mice with selective overexpression of angiotensinogen in adipose tissue develop obesity with a high-fat diet and especially hypertension, which is compatible with involvement of adipose-tissue angiotensinogen secretion in the genesis of this phenotype (95).

Omentin

Omentin is a secretory protein that has been recently identified as a new adipokine encoded by two genes (1 and 2) that is highly and selectively expressed in visceral adipose tissue. Omentin may regulate insulin action. Omentin 1 plasma levels and adipose tissue gene expression are decreased with obesity, and they correlate positively with plasma adiponectin and high-density lipoprotein and negatively with waist circumference, BMI, and insulin resistance (96). Omentin transcripts are strongly expressed in visceral adipose tissue, but poorly in subcutaneous fat. Omentin is present in the stromal vascular cells of omental adipose tissue, but not in mature fat cells. Human omentin is a peptide of 313 amino acids, and contains a secretory signal sequence and a fibrinogen-related domain (97). It is secreted in the culture medium of omental, but not subcutaneous, fat explants. Interestingly, it increases insulin-stimulated glucose uptake in both omental and subcutaneous adipocytes, and promotes Akt phosphorylation (98).

Chemerin

Chemerin is a novel and promising adipokine, whose plasma levels in humans have been found to be significantly associated with BMI, circulating triglycerides, and blood pressure (99). It has been demonstrated that chemerin or chemerin receptor knockdown impairs differentiation of 3T3-L1 cells into adipocytes, reduces the expression of adipocyte genes involved in glucose and lipid homeostasis, including adiponectin and leptin, and alters metabolic functions in mature adipocytes (100).

Apelin

Apelin is an adipokine produced and secreted by adipocytes, whose plasma levels are significantly elevated by obesity and insulin in humans, which was found to be the endogenous ligand for the G protein-coupled APJ receptor. The gene that encodes the apelin receptor shares the greatest sequence identity with the angiotensin AT1 receptor (101). Apelin production is up-regulated by hypoxia. Apelin has been shown to exert potent positive inotropic effects on both normal and failing myocardium. The cardiac apelin system

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is down-regulated by angiotensin II, and its restoration is reached by treatment with angiotensin type 1 receptor blocker.

Vaspin

Vaspin is an adipokine recently identified as a member of the serine protease-inhibitor family (102). It is strongly expressed in visceral adipose tissue and is stimulated in mouse and human obesity (103). Its tissue expression and plasma levels are normalized in the presence of insulin or an insulin-sensitizing drug (pioglitazone) (104).

Serum amyloid A

Serum amyloid A (SAA) is an inflammatory acute-phase protein associated with systemic inflammation and atherosclerosis, and is used as a predictive marker in coronary accidents or cardiovascular events. Circulating levels of SAA are significantly correlated with insulin resistance in obesity and type 2 diabetes (105). SAA is expressed in adipose tissue, and this expression is largely increased in obesity and diabetes (106,107). Also, SAA could participate in lipoprotein metabolic alterations, promoting the linking of HDL-cholesterol to macrophages, thus reducing their cardiovascular-protective effect.

C-reactive protein

C-reactive protein (CRP) mRNA is detected in adipocytes. Adiponectin knockout mice show higher plasma CRP levels than wild-type mice. There is a strong negative correlation between adiponectin mRNA and CRP mRNA expression in human adipose tissue suggesting that a decrease in adiponectin leads to a rise in CRP. CRP can inhibit insulin-evoked NO production in endothelial cells through specific inactivation of the PI3K/Akt/eNOS pathway (108,109). Similar to TNF-α, CRP simultaneously increases endothelial ET-1 production (109).

Thrombospondin-1 and CD36

One of the newer adipokines is Thrombospondin-1 (TSP1), a multi-domain, multi-functional glycoprotein synthesized by many cell types, which modulates cell adhesion and proliferation. Thrombospondin-1 is a major activator of TGF-β1 *in vivo* (110). As a result, TSP1 is involved in angiogenesis, inflammation and wound healing. CD36 is the receptor for thrombospondin-1 and is present on platelets, mononuclear phagocytes, adipocytes, hepatocytes, myocytes, and some epithelia (111). On phagocytes, it functions as a scavenger receptor, recognizing specific oxidized phospholipids and lipoproteins. CD36 also binds long-chain fatty acids and facilitates their transport into cells, thus participating in muscle lipid utilization, adipose energy storage, and gut fat absorption and possibly contributing to the pathogenesis of metabolic disorders, such as diabetes and obesity. The chemotactic properties of TSP-1 (112) provide a link between TSP1 and macrophage-mediated adipocyte inflammation. In addition, adipocyte-macrophage co-culture experiments demonstrated TSP1 gene and protein up-regulation by both cell types, suggesting a feed-forward inflammatory mechanism in adipose tissue (113). TSP1 may be an important component of inflammation and coagulation in the metabolic complications of obesity.

INSULIN RESISTANCE AND HYPERGLYCEMIA

Insulin resistance

Insulin resistance is the second key biological component of the metabolic syndrome. Chronic inflammation associated with visceral obesity induces insulin resistance in the liver (34). This chronic inflammation is characterized by the production of abnormal adipokines and cytokines such as TNF-α, FFA, IL-1, IL-6, leptin and resistin. These factors inhibit

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insulin signaling, which in turn causes impaired suppression of glucose production by insulin in hepatocytes, leading to hyperglycemia. An important and early complication of hepatic insulin resistance is the induction of hepatic VLDL production, via changes in the rate of apoB synthesis and degradation and *de novo* lipogenesis, or increased free fatty acid flux from adipose tissue into the liver. Insulin resistance also stimulates the production of CRP and PAI-1, both markers of an inflammatory state. All metabolic abnormalities related to hepatic insulin resistance have been shown to directly or indirectly promote atherosclerosis. Insulin has several direct vascular actions that contribute to either vascular protection or injury, depending on the cell type. Vascular protective effects of insulin include stimulation of endothelial cell production of the vasodilator nitric oxide. This, in turn, inhibits formation of lesions dependent on migration and proliferation of vascular smooth muscle cells, attenuates binding of inflammatory cells to the vascular wall, and inhibits thrombosis by reducing platelet adhesion and aggregation. However, insulin also promotes a host of deleterious vascular effects by stimulating the actions of various growth factors including angiotensin II and PAI-1. Glucocorticoid metabolism is also abnormal in insulin-resistant states. Adipocyte-derived hormones, including adiponectin and leptin, regulate systemic insulin sensitivity in accordance to existing triglyceride reserves. Leptin levels reflect existing fat mass and the adipokine negatively regulates insulin action in adipose tissue. Adiponectin, on the other hand, preserves insulin sensitivity via transient increments of AMPK activity and its circulating levels seem to reflect the adipogenic capacity of adipose tissue. Due to the fact that adiponectin and insulin are synergistic, inadequate adiponectin production contributes to systemic insulin resistance. In insulin-resistant states associated with impaired PI3K-dependent insulin signaling pathways, insulin-mediated ET-1 secretion is augmented and blockade of ET-1 receptors significantly improves insulin sensitivity and peripheral glucose uptake in the context of insulin resistance (114,115).

Elevated blood glucose levels induce a series of alterations within the vasculature including endothelial dysfunction, cellular proliferation, changes in extracellular matrix conformation and impairment of LDL receptor-mediated uptake decreasing the *in vivo* clearance of LDL concentrations (116–120). The presence of high glucose concentrations also increases lipoprotein oxidation (121). Elevated glucose leads to the activation of the sorbital pathway, cellular oxidative stress and formation of advanced glycation endproducts (AGE). AGE can be processed by macrophages through a recently characterized series of high-affinity receptors: scavenger receptors types I and II, the receptor for advanced glycation endproducts (RAGE), oligosaccharyl transferase-48 (OST-48, AGE-R1), 80K-H phosphoprotein (AGE-R2) and galectin-3 (AGE-R3). Coupling of AGE proteins to their AGE receptor results in TNF-α and IL-1 synthesis and secretion. Evidence provided by both clinical and pre-clinical studies regarding a central involvement of the receptor for advanced glycation endproducts (RAGE) in vascular disease continues to mount. RAGE is upregulated as a consequence of diverse inflammatory stimuli including hyperglycemia, oxidized low density lipoprotein (oxLDL) and reduced shear stress. RAGE may maintain and amplify inflammatory responses in the vasculature if ligand for the receptor is present. RAGE binding by circulating AGEs or S100 protein released by activated leukocytes results in the generation of reactive oxygen species (ROS) and further activation of NF-αB. This leads to upregulation of adhesion molecules for circulating monocytes as well as further upregulation of RAGE itself. In addition, these ROS may scavenge and reduce bioavailability of the labile vasodilator NO, reducing its anti-inflammatory effects and possibly compromising control of vascular tone directly.

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ENDOTHELIAL DYSFUNCTION AND INFLAMMATION

Adipose tissue resident macrophages and adipocytes in the adipose tissue and the consequences of hyperglycemia, altered lipoproteins and hyperinsulinema in the vasculature and within organ microcirculations induce dysfunctional endothelia and a pro-inflammatory state in metabolic syndrome (122).

Endothelial dysfunction

Endothelial dysfunction is an important component of the metabolic syndrome. Deficiency of endothelial-derived NO is believed to be the primary defect that links insulin resistance and endothelial dysfunction. NO deficiency results from decreased synthesis and/or release, in combination with exaggerated consumption in tissues by high levels of reactive oxygen and nitrogen species due to cellular disturbances in glucose and lipid metabolism. Insulin may stimulate endothelial nitric oxide production or may act directly on vascular smooth muscle via stimulation of the Na^+-H^+ exchanger and Na^+/K^+-ATPase, leading to hyperpolarization of the cell membrane and consequent closure of voltage-gated Ca^{2+} channels. Endothelial dysfunction contributes to impaired insulin action by altering the transcapillary passage of insulin to target tissues. Reduced expansion of the capillary network, with attenuation of microcirculatory blood flow to metabolically active tissues, contributes to the impairment of insulin-stimulated glucose and lipid metabolism. Insulin-induced vasodilation, which is mediated by the release of NO, is impaired in obese individuals who display insulin resistance, possibly due to suboptimal levels of (6R)-5,6,7,8-tetrahydrobiopterin (BH_4), the natural and essential cofactor of NO synthases (NOS), and accelerated inactivation of NO by O^{2-} within the vascular wall was observed. A 'third factor' may cause both insulin resistance and endothelial dysfunction in cardiovascular disease. Candidates include skeletal muscle fibre type and capillary density, distribution of adiposity and endogenous corticosteroid production. A complex interaction between endothelial dysfunction, abnormal skeletal muscle blood flow and reduced insulin-mediated glucose uptake may be central to the link between insulin resistance, blood pressure, impaired glucose tolerance and the risk of cardiovascular disease.

TNF-α

Of the pro-inflammatory cytokines, TNF-α is the best described in disturbed insulin signaling. Mice lacking TNF-α or TNF-α receptors are resistant to the development of obesity induced insulin resistance (123,124). In adipose tissue, TNF-α is mostly secreted by macrophages in the stromal vascular fraction. Circulating TNF-α and adipose tissue TNF-α gene expression are increased in insulin resistance (125), and acute infusion of TNF-α inhibited insulin-induced glucose uptake in healthy subjects (126). Neutralization of TNF-α in rodents has improved insulin resistance (127), whereas attempts to neutralize TNF-α in humans to improve insulin resistance have generally not been successful (128)), although more recent studies have shown slight improvement in insulin resistance with TNF-α inhibition (129–131). Limited effects of TNF-α blockade on insulin resistance could be explained by the paracrine actions of TNF-α. Further investigations on the mechanisms involved in TNF-α overexpression associated with obesity and molecular signals underlying TNF-α-induced metabolic dysregulation are warranted. TNF-α increases ET-1 secretion and inhibits insulin's stimulating effect on endothelium-dependent vasodilation in humans (132,133).

IL-6

IL-6 is also overexpressed in adipose tissue of the obese (125). The role of IL-6 in metabolic changes associated with obesity is unclear. There are some reports of IL-6 causing impaired insulin signaling in the liver and adipocytes by inducing ubiquitin-mediated degradation of

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insulin receptor substrate through suppressor of cytokine signaling (SOCS) 1 and 3 (134,135). However, effects of IL-6 on insulin sensitivity in skeletal muscle are controversial (135). Exercise that is associated with increased insulin action in skeletal muscle increases circulating IL-6 levels dramatically (136), suggesting possible anti-inflammatory roles for IL-6 in skeletal muscle. The data on the increased onset of obesity and diabetes in mice lacking IL-6 are conflicting (137,138). IL-6 also inhibits insulin-stimulated increases in eNOS activity and NO production in the endothelium (139). IL-1 together with IL-6 concentrations reportedly predicts the risk for Type 2 diabetes in humans better than either cytokine alone (140).

IL-10

Decreased production of IL-10, an anti-inflammatory cytokine, has been associated with the development of Type 2 Diabetes, and IL-10 plasma levels can be positively correlated with insulin sensitivity (141,142). Lower IL-10 levels have been associated with the metabolic syndrome in obese, insulin-resistant postmenopausal women compared with women who are obese but do not satisfy the criteria for metabolic syndrome (143). IL-10 decreases IL-6-induced insulin resistance in muscle and liver in mice co-treated with IL-6 and IL-10 (144). A recent study showed that IL-10 is expressed in macrophages derived from adipose tissue and that the IL-10 receptor is expressed in adipocytes and not immune or endothelial cells in fat (145). Several studies indicate that IL-10 is an anti-inflammatory factor produced by immune cells in adipose tissue that acts on adipocytes to improve insulin signaling, potentially decreasing further macrophage recruitment.

MCP

Adipocytes secrete various chemoattractants that draw monocytes from circulation into adipose tissue. MCP-1, also known as chemokine (C-C motif) ligand 2 (CCL-2), is one the chemoattractants that plays an important role in the recruitment of macrophages to the adipose tissues. Moreover, obesity is associated with increased plasma levels of MCP-1 and overexpression in adipose tissue (146,147). Mice lacking MCP-1 receptor (CCR-2) have decreased adipose tissue macrophage infiltration and improved metabolic function (148,149). Other candidates might likely contribute to the recruitment of macrophages into the adipose tissue, such as macrophage inflammatory protein-1 (150) and osteopontin (151,152). Osteopontin is an extracellular matrix protein that promotes monocyte chemotaxis, and the lack of osteopontin in mice caused improved insulin sensitivity and decreased macrophage infiltration into adipose tissue (152).

HYPERTENSION

Essential hypertension is a complex, multi-factorial, quantitative trait under polygenic control. Increased peripheral resistance due primarily to changes in vascular structure and function appear to be the fundamental hemodynamic abnormality in hypertension. These changes include arterial wall thickening and abnormal vascular tone, and are due to alterations in the biology of the cellular and non-cellular components of the arterial wall. Multiple interacting humoral and mechanical factors as well as oxidative stress stimulate complex signaling pathways, which modulate vascular smooth muscle cell contraction and growth (153). Hypertension is one of the commonest components of metabolic syndrome and is linked to both essential hypertension and obesity-related hypertension (154). Excess weight gain is likely the major cause of essential hypertension, and abnormal kidney function appears to be a cause as well as a consequence of obesity hypertension. Excess renal sodium re-absorption and a hypertensive shift of pressure natriuresis play a major role in mediating increased blood pressure associated with weight gain. Activation of the renin-

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angiotensin and sympathetic nervous systems and physical compression of the kidneys appear to contribute to obesity-induced increases in sodium re-absorption and hypertension.

COAGULATION

Fibrinolytic dysfunction mediates the increased risk of coronary artery disease in individuals with the metabolic syndrome (155). Adipose tissue induces thrombocyte activation by the production of adipokines, of which some such as leptin and adiponectin have been shown to directly interfere with platelet function. Increased adipose tissue mass induces insulin resistance and systemic low-grade inflammation, also affecting platelet function. It has been demonstrated that adipose tissue directly impairs fibrinolysis by the production of plasminogen activator inhibitor-1 and possibly thrombin-activatable fibrinolysis inhibitor (156). Adipose tissue may contribute to enhanced coagulation by direct tissue factor production, but hypercoagulability is likely to be primarily caused by altered hepatic synthesis of the coagulation factors fibrinogen, factor VII, factor VIII and tissue factor, by releasing free fatty acids and pro-inflammatory cytokines (TNF-α, IL-1 and IL-6) into the portal circulation and by inducing hepatic insulin resistance. Adipose tissue dysfunction could thus play a causal role in the prothrombotic state observed in obesity, by directly and indirectly affecting hemostasis, coagulation and fibrinolysis (157).

In type 2 diabetes, there are increased levels of fibrinogen and PAI-1, favoring both thrombosis and defective dissolution of clots once formed. Platelets in type 2 diabetic individuals adhere to vascular endothelium and aggregate more readily than those in healthy people. Loss of sensitivity to the normal homeostatic restraints exercised by prostacyclin (PGI_2) and nitric oxide (NO) generated by the vascular endothelium presents as the major defect in platelet function. Insulin is a natural antagonist of platelet hyperactivity. It sensitizes the platelet to PGI_2 and enhances endothelial generation of PGI_2 and NO. Thus, the defects in insulin action in diabetes create a milieu of disordered platelet activity conducive to macrovascular and microvascular events (158). Patients with type 2 diabetes and abdominal fat patterning displayed higher plasma activities of clotting factors VII and VIII as well as increased plasma levels of fibrinogen and von Willebrand factor antigen, when compared with not only healthy normal weight controls, but also with diabetic patients at normal body weight (159,160).

PAI-1 is elevated in subjects with the metabolic complications of obesity, and is expressed in the stromal fraction of adipose tissue, including endothelial cells (161–165). PAI-1 inhibits both tissue-type plasminogen activator and urokinase-type plasminogen activator through its serine protease inhibitor function, and thus contributes to a pro-thrombotic state (166). PAI-1 gene expression is controlled by TGF-β, which combines with phosphorylated SMAD and binds to the PAI-1 promoter (167). A second pathway is via TSP1. TSP1 is expressed in adipocytes (113) and inhibits angiogenesis, cell proliferation, and wound healing (112,168). TSP1 is a major activator of TGF-β R1 (110), and PAI-1 activation by TSP1 has been described (169). A recent study demonstrated TSP1 expression largely by adipocytes compared with the stromal vascular fraction of adipose tissue, suggesting that TSP1 is a true adipokine(113). TSP1 expression was increased in obese, insulin-resistant subjects, was associated with plasma PAI-1 levels, and was positively associated with adipose tissue macrophage markers. In addition, TSP1 expression was decreased by treatment of subjects or adipocytes with the PPAR-γ agonist, pioglitazone.

Modeling Metabolic Syndrome

The ideal model for metabolic syndrome should be obese, hypertensive, insulin resistant and have the appropriate dyslipidemia. There is at present no perfect animal model of this human disease. The most common models to study metabolic syndrome are mice which can be

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based one of three strategies: obese mouse strains that mimic metabolic syndrome; mice fed high-fat diets to induce metabolic syndrome; or gene knockout mice that mimic metabolic syndrome. Insulin resistance in mice with differential susceptibility to diabetes and metabolic syndrome is preceded by differences in the inflammatory response of adipose tissue. This phenomenon may serve as an early indicator of disease and contribute to disease susceptibility and progression (170). The $Lep^{ob/ob}$, $LepR^{db/db}$ and $A^{y/a}$ mice are the three most commonly used spontaneously mutant obese mouse models. They display insulin resistance and may develop diabetes depending on the background strain. In addition, $A^{y/a}$ mice have intact leptin signaling and display a delayed onset obesity that can be amplified by high-fat feeding, making them a good model for human obesity. All three models fall short of an ideal model for metabolic syndrome (171). Obese mouse models such as $A^{y/a}$, $Lep^{ob/ob}$ and $LepR^{db/db}$ have increased total plasma cholesterol levels; however, this is the result of increased HDL rather than increased VLDL and LDL levels. The increase in HDL makes these mice resistant to atherosclerotic lesion formation. These lipid changes do not mirror those seen in metabolic syndrome. Hypertensive mice do not make good models unless cross bred with obese mice (171). Care should thus be taken to choose the mouse model most appropriate for the scientific or mechanistic mechanism to be tested under metabolic syndrome conditions.

Conclusion

Metabolic syndrome represents a combination of synergistic vascular pathologies that lead to an accelerated atherogenic state that compromises the ability of the patient to satisfactorily respond to humoral, cellular and mechanical stresses. Delineating the contribution of insulin resistance and the role of the adipokines remains a focus of current research. Defining key signaling pathways may provide opportunities for new therapeutic targets and interventions. It represents a complex pathology that will require better definition prior to the development of satisfactory therapeutic interventions.

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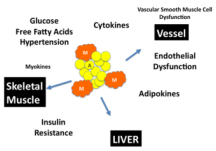

Figure 1.

Metabolic syndrome is characterized by atherogenic dyslipidemia (low high density lipoprotein and high triglycerides levels), elevated blood pressure, elevated plasma glucose, a prothrombotic state, and a pro-inflammatory state. This is a result of an increase in adipocyte mass (A) and infiltration of macrophage infiltration (M) in the fat tissue and in organs. The presence of elevated blood pressure, elevated blood glucose and serum free fatty acids, hyperinsulinemia and insulin resistance leads dysfunction in skeletal muscle, liver and microcirculations. The secretion of myokines, adipokines and cytokines acts synergistically to enhance the metabolic state and drive the end-organ dysfunction.

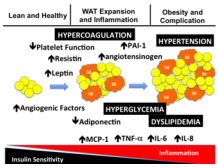

Figure 2.

The development of metabolic syndrome is a journey from lean and healthy to white adipose tissue (WAT) expansion and inflammation which progresses to obesity and its associated complications. Expansion of the WAT is associated with an angiogenic response and an increase in the infiltration of macrophages into the WAT. The visceral and truncal WAT alter their production of adipokines and cytokines which leads to enhanced inflammation and a loss of insulin sensitivity (development of insulin resistance). The result of the changes in adipokines and cytokines leads to hypertension, hyperglycemia, dyslipidemia and a hypercoaguable state

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Table 1

Definitions of Metabolic Syndrome

	NCEP ATP III	WHO
Absolutely required	None	Insulin resistance* (IGT, IFG, T2D or other evidence of IR)
Criteria	Any three of the five criteria below	Insulin resistance or diabetes, plus two of the five criteria below
Obesity	Waist circumference: >40 inches (M), >35 inches (F)	Waist/hip ratio: >0.90 (M), >0.85 (F); or BMI >30 kg/m^2
Hyperglycemia	Fasting glucose 100 mg/dl or On Therapy	Insulin resistance already required
Dyslipidemia	Triglycerides ≥150 mg/dl or On Therapy	Triglycerides ≥150 mg/dl or HDL-C: <35 mg/dl (M), <39 mg/dl (F)
Dyslipidemia (second, separate criteria)	HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F) or On Therapy	
Hypertension	>130 mmHg systolic or >85 mmHg diastolic or On Therapy	≥140/90 mmHg

* IGT, impaired glucose tolerance; IFG, impaired fasting glucose;

T2D, type 2 diabetes; IR, insulin resistance.

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Table 2

Signaling molecules of Metabolic Syndrome

CYTOKINES	ADIPOKINES	COAGULATION	HYPERTENSION	ADIPOCYTE RELATED
TNF-α	Leptin	PAI-1	Angiotensinogen	Acylation Stimulating Protein
IL-6	Adiponectin	Tissue Factor	Prostaglandins	Monobutyrin
IL-8	Resistin	TIMP-1	Oxygen Free Radicals	Adipsin
IL-10	Visfatin			Adiophilin
L-1Rα	Apelin			ApoE
L-1RA	Vaspin			Pentraxin-3
TGF-β	Chemerin			SAA
IGF1	Hepcidin			Agouti
HBEGF	RBP-4			α1 acid glycoprotein
MCP-1	Omentin			