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Adipokine Dysregulation and Insulin Resistance with Atherosclerotic Vascular Disease: Metabolic Syndrome or Independent Sequelae?

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Abstract

Adipokine dysregulation and insulin resistance are two hallmark sequelae attributed to the current clinical definition of metabolic syndrome (MetS) that are also linked to atherosclerotic vascular disease. Here, we critically discuss the underlying pathophysiological mechanisms and the interplay between the two sequelae. Adipokine dysregulation is involved with decreased nitric oxide, vascular inflammation, and insulin resistance in itself to promote atherosclerosis. Insulin resistance is involved with endothelial dysfunction by direct and indirect mechanisms that also promote vascular inflammation and atherosclerosis. These mechanisms are discussed in atherosclerosis irrespective of MetS, and to evaluate the possibility of synergism in MetS. High retinol binding protein-4 (RBP-4) and low cholesterol efflux in MetS may provide evidence of possible synergism and elevated atherosclerotic risk. An adverse adipokine panel that includes fetuin-A and adiponectin can potentially assess atherosclerotic risk in even those without MetS. Genetic possibilities may exist in atherosclerotic vascular diseases secondary to insulin resistance.

Keywords

Adipokines; Atherosclerosis; Endothelial dysfunction; Inflammation; Insulin resistance; Metabolic syndrome

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Introduction

In a joint statement from the American Diabetes Association (ADA) and European Association for The Study of Diabetes (EASD) in 2005, the metabolic syndrome (MetS) is argued to be imprecisely defined and with a considerable doubt that it is a risk factor for cardiovascular disease.[1] However, the MetS, which has been linked to obesity, is characterized by a cluster of risk factors for atherosclerosis such as hypertension, dyslipidemia and elevated blood glucose, and has also been claimed to be an independent risk factor for cardiovascular disease and stroke.[2,3] Currently, the understanding of this cluster of risk factors as a 'syndrome' is subject to debate, with increased risk attributable to the syndrome to be controversial, compared to the individual risk of each factor. Nevertheless, adipokine dysregulation and insulin resistance, two hallmark sequelae presumably resulting from the MetS cluster, have been linked to vascular inflammation and endothelial dysfunction, and increased levels of inflammatory markers, collectively increasing the risk of atherosclerosis and harmful vascular remodeling.[4] While many non-vascular sequelae have been attributed to MetS, the purpose of this critical review is twofold. The first is to discuss the pathophysiological mechanisms of adipokine dysregulation and insulin resistance, two primary issues believed to be working in concert in MetS, in relation to atherosclerotic vascular disease (AVD) from our presumed understanding of MetS. The second is to utilize our knowledge from this pathophysiology to evaluate and refine diagnostic routes for AVD from the independent identification of these two hallmark sequelae, but also whether the possibility of true synergism for AVD risk in MetS exists. As the prevalence of obesity increases in the United States, and therefore potentially adipocyte dysfunction, insulin resistance and adipokine dysregulation will become an even greater health care problem that will require aggressive screening of patients with optimized treatment. Similarly, the co-occurrence of the risk factors within the MetS diagnostic cluster that promote these sequelae, whether independently or synergistically, can be appreciated by the prevalence of MetS in the general adult population that has increased from 25.3% (1988–1994) to 35% (2007–2012) in the United States.[5]

Historical Perspective

The term "metabolic syndrome" first appeared in literature in the 1950s when researchers identified risk factors for the progression and development of type 2 diabetes.[6] The current concept of metabolic syndrome began to take shape in the 1970s. In 1977, Haller[7] and Singer[8] used the term "metabolic syndrome" in association with obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia, steatohepatitis and atherosclerosis. One year later, Gerald Phillips[9] recognized that there is an array of risk factors associated with myocardial infarction, such as glucose intolerance, hyperinsulinemia, hyperlipidemia and hypertension. It was hypothesized that sex factors are accountable for this relationship. In 1988, Reaven[6] reevaluated this hypothesis and proposed that insulin resistance was the underlying cause of hyperinsulinemia, hyperlipidemia and hypertension (i.e., the metabolic syndrome). More recently, the term "metabolic syndrome" has been used interchangeably with several other terms such as insulin resistance syndrome, Reaven's syndrome and syndrome X. These all refer to a combination of disorders that increase an individual's risk of cardiovascular

disease and diabetes, with adipokine dysregulation and insulin resistance implicated at the heart of the disorder.

Diagnostic Criteria for MetS

The diagnostic criteria for MetS was developed to improve understanding of the link between insulin resistance and vascular disease. At first, there was no consensus on a definition for metabolic syndrome. Currently, there are five definitions of the MetS as described by the World Health Organization (WHO), International Diabetes Federation (IDF), American Association of Clinical Endocrinologists (AACE), European Group for the Study of Insulin Resistance (EGIR) and National Cholesterol Education Program (NCEP). In 2002, the NCEP Adult Treatment Panel III (NCEP ATP III) proposed a revised definition of the MetS that could be easily measured in clinical practice.[10] Emphasizing the risk of cardiovascular disease, ATP III criteria define the MetS as the presence of any three of five traits described in Table 1, and is the most widely used.[11] While many patients with type 2 diabetes may have similar traits, the co-occurrence with MetS is believed to confer a greater risk for macrovascular over microvascular complications.[12] The interplay of these criterion of MetS on AVD (Figure 1) is believed to evolve into two major events – adipokine dysregulation and insulin resistance, each of which may occur individually and not in the context of a syndrome at all.

Pathophysiology of the Adipokine Dysregulation and Atherosclerotic Vascular Disease

The role of adipokine dysregulation in promoting atherosclerosis is briefly summarized in Figure 2. A group of adipose tissue generated cytokines, collectively termed as adipokines that have both local and systemic effects, promote atherosclerosis. Furthermore, the dysregulation of adipokines has been implicated in obesity, type 2 diabetes, and MetS, where overproduction comes secondary to increased adiposity.[13] On the contrary, the reduction in certain adipokines, such as adiponectin, has been linked to insulin resistance and decreased production of nitric oxide in vascular endothelial cells, thus promoting atherosclerosis. However, the control of various adipokine production remains unknown and an interest for future research and intervention.

Tumor necrosis factor-alpha (TNF-α) is one adipokine that is seen in greater serum levels in patients with the diagnostic profile of MetS and provides evidence for inflammation that underlies atherosclerosis and promotes insulin resistance independently.[14] Similarly, TNF-α has also been associated with stages of early atherosclerosis in humans.[15] Within ApoE-deficient mice, the dysregulation of TNF-α upregulates the expression levels of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemoattractant protein-1 (MCP-1) implicating an atherogenic role with scavenger receptor class A (SRA) expression and oxidized low-density lipoprotein (LDL) uptake in macrophages.[16] MCP-1 potentiates the atherogenic role with the recruitment of monocytes/macrophages into the arterial vessel wall and has been shown to be elevated in patients with coronary artery disease (CAD).[17] In the continuation of a chronic inflammatory state, TNF-α can also induce synthesis of another adipokine, plasminogen

activator inhibitor - 1 (PAI-1) leading to a pro-thrombotic state that can independently promote atherosclerosis through smooth muscle migration and changes in matrix degradation within vasculature.[18] PAI-1 is an inhibitor of plasminogen activators (urokinase and tissue types) and vitronectin, and exhibits circadian release that may explain the occurrence of myocardial infarction and stroke in the early morning hours.[19] Other inducers of PAI-1 exist with strong evidence among many of the MetS ATP III defining criteria (mean arterial pressure (MAP), high-density lipoprotein (HDL) cholesterol, triglycerides, and fasting plasma glucose), in addition to very low-density lipoprotein (VLDL) cholesterol and angiotensin II, offering a potential link between MetS and atherosclerosis.[20–22]

Hypertension is associated with lower wall shear stress, which is known to be associated with the development of atherosclerosis and vascular remodeling secondary to inflammation of the vessel wall with cell proliferation and thrombosis.[23–26] As an adipokine as well, the major extrahepatic production of angiotensinogen (AT) by adipose tissue is increased in obesity and provides another link between adipocyte dysfunction or MetS, with vascular sequelae and subsequent hypertension.[27] Additionally, the relationship of AT from adipose tissue and atherosclerosis seems to be mediated mostly by the angiotensin II (Ang II) intermediate.[27–28] Supported by *Ldlr−/−*mice with a lack of bone marrow C-C chemokine receptor type 2 (CCR2), Ang II is believed to promote the differentiation of monocytes from progenitor cells and upregulate CCR2, which recruits the inflammatory milieu that promotes atherosclerosis.[29–31] Furthermore, in understanding such hypertension to be obesity-related, differential activation of the renin-angiotensin system (RAS) within the microvasculature of visceral adipose tissue may underlie the systemic hypertension seen in obesity or MetS.[32] In a study of obese human subjects undergoing elective bariatric surgery, visceral arterioles in hypertensives had significantly greater Ang-II mediated vasoconstriction than normotensives, and was selectively greater than subcutaneous arterioles. Antagonistic to the actions of AT, apelin (secreted by mature adipocytes with a G-protein coupled apelin receptor - AJP) is a lesser known adipokine that has been implicated in MetS (in the context of adipokine dysregulation) with the ability to counteract Ang II signaling seen in atherosclerotic mice models.[33–35] However, higher levels of apelin have been discovered in clinical MetS and obesity, and may reflect endothelial damage with vasoconstriction via apelin receptors in vascular smooth muscles.[36] Nevertheless, such variability in physiologic response is not fully appreciated in the context of adipocyte dysregulation, with or without MetS, and is worth inquiry given the associations of the apelinergic system with type 2 diabetes mellitus, hypertension, and heart failure.[37–38]

In the Third Generation Cohort of the Framingham Heart Study, higher levels of adipokines, retinol-binding protein-4 (RBP-4) and fetuin-A, marked future cardiometabolic risk and the incidence of clinical MetS.[39] RBP-4 is a protein with retinol transport function that has been implicated in insulin resistance, which can promote vascular inflammation.[40] However, the mechanism of this connection between RBP-4 and insulin resistance is less known. Fetuin-A is another adipokine protein that also promotes insulin resistance through inhibition of insulin receptor's tyrosine kinase activity and is likewise also associated with vascular disease.[41–42] Notably from this Framingham Heart study, RBP4 levels were elevated independently of obesity and may potentially be a unique biomarker of MetS, providing evidence of such a syndrome as well. Therefore, in the absence of obesity, this may raise the

possibility of overlapping mechanisms of insulin resistance by other MetS criteria and RBP-4, if not interrelated. Furthermore, other components of the adverse adipokine profile noted in incident MetS within the study were higher levels of fetuin-A and lower levels of adiponectin, the latter of which was notably lower in metabolically healthy obese patients (those without MetS) in comparison.

Adiponectin is an adipokine protein that interacts with distinct G-protein coupled receptors (GPCRs), AdipoR1 and AdipoR2, where its binding associates with intracellular protein adaptor protein phosphotyrosine interacting with plekstrin homology domain and leucine zipper 1 (APPL1) to improve insulin sensitivity and promote anti-inflammatory response, fatty acid oxidation and increased endothelial nitric oxide synthase (eNOS) vasodilatory activity.[43] Focusing on the anti-atherosclerotic potential of adiponectin, the inhibition of downstream components of nuclear factor-kappa beta (NF-kB) and other factors may explain the anti-inflammatory mechanism as noted in apoE-deficient mice.[44] A second anti-atherosclerotic mechanism of adiponectin may also be explained by its ability to improve endothelial function by the upregulation of eNOS and the inhibition of inducible NOS (iNOS) activity in vasculature to limit hyperlipidemic vessel injury.[45] Adiponectin has also been implicated in limiting further plaque progression with decreased adhesion capacity to vascular endothelial cells, decreased migration of smooth muscle cells, and decreased oxidation of lipids within macrophages (foam cells).[46–47]

Quite the contrary to adiponectin, leptin, while also involved in energy homeostasis, is speculated to be involved in the pathogenesis of atherosclerosis through enhanced inflammatory cytokine production (perhaps through stimulating a Th1 phenotype in helper cells)[48], vascular smooth muscle cell migration and proliferation (mediated by mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3-K) activation)[49–50], vessel wall angiogenesis, and increased oxidative stress in endothelial cells (with reduction in nitric oxide (NO) bioactivity and increased expression of MCP-1).[51] However, in a recent meta-analysis, high leptin levels were not associated with risks of cardiovascular disease or stroke and may reflect the dominant role played by weight in the leptin pathway, as indicated by the findings of the Framingham Heart Study as well.[39,52] Unlike the evidence surrounding adiponectin, the implications of leptin, beyond MetS, to link adipocyte dysregulation and AVD are less well known.

Insulin Resistance and Endothelial Dysfunction in Atherosclerotic Vascular Disease

The role of insulin resistance in promoting atherosclerosis is briefly summarized in Figure 3. Seen in diabetes and likewise considered in MetS, endothelial dysfunction is one of the earliest events of insulin resistance promoting AVD and is an area of therapeutic intervention that is not well-understood.[53] Stemming from adipokine dysregulation, hyperinsulinemia and hyperglycemia associated with increased insulin resistance facilitates the release of vasoconstrictors and inflammatory markers in promoting endothelial dysfunction. Additionally, dyslipidemia abnormalities secondary to insulin resistance, or as part of the MetS cluster further potentiate endothelial dysfunction.[54] Endothelial homeostasis is a

balance between mediators that promote vasodilation (e.g., NO or prostacyclin (PGI2) and vasoconstriction (e.g, Ang II or ET-1), both of which are altered by insulin.[55–56] Endothelial cell dysfunction is an initial step in atherosclerosis that involves a phenotypic change within cells that alters vascular tone and redox balance, in addition to acute and chronic inflammatory control responsible for hemostasis and thrombosis.[57] Likewise, as reviewed by Gimbrone and Cardena (2017), the link between atherosclerosis with endothelial proinflammatory activation and endothelial cell dysfunction is mediated by: (i) Selective adhesivity of VCAM-1 for mononuclear leukocyte and lymphocyte recruitment, (ii) Intrinsic capacity of activated vascular endothelium to secrete chemokines, disrupting a balance between inflammatory mediators (e.g, IL-1) and anti-inflammatory mediators (e.g., specialized pro-resolving mediators [SPMs]), (iii) Upregulation of endothelial NF-kB, which may promote changes in endothelial chromatin, and (iv) Distinct hemodynamic forces with dysregulation of specific shear stress response elements (e.g, NO), which can serve as a focal risk factor. However, genetic considerations that might surround resolution deficits long after endothelial cell dysfunction are warranted.

As a part of the normal function of insulin, activation of membrane-bound eNOS and the subsequent synthesis of NO by insulin binding allows for vasodilation.[55,58] This action is mediated by the activation of the PI3-K/Akt pathway and phosphorylation of eNOS, promoting the conversion of L-arginine to L-citrulline and NO. However, in insulin resistance seen in cardiometabolic disorders such as MetS, the response is the opposite, where vasoconstriction ensues for reasons that are multifactorial.[59] Abnormal pteridine metabolism has been linked to decreased NO production and endothelial dysfunction in insulin-resistant patients.[60] The mechanism is believed to involve tetrahydrobiopterin depletion (BH_4), an activating cofactor of NOS, and elevation of 7,8-dihydrobiopterin (BH_2), an inactivating cofactor of NOS, leading to a decrease in NOS activity and impairment of vasodilation with increased superoxide anion generation.[61] Furthermore, the hyperglycemia that ensues from insulin resistance impairs activation of PI3-K and phosphorylation of eNOS by activation of the hexosamine biosynthesis pathway, leading to modification in insulin proteins, decreased NO signaling by O-Glc-N-acylation of insulin receptor substrate-1 (IRS-1) adaptor protein and formation of advanced glycation end products (AGEs) that stimulate reactive oxygen species (ROS).[62,63] Additionally, the production of AGEs inhibit the PI3-K/Akt pathway by activation of protein kinase C (PKC) (through increased synthesis of diacylglycerol), and the subsequent ROS produced activate NF-kB and inflammatory mediators via stimulation of inhibitor of nuclear factor kappa-B kinase subunit beta (IKKB kinase-β).[64,65] PKC activation promotes production of both pro-thrombotic and growth factors, and induces the formation of the vasoconstrictor, endothelin-1 (ET-1).[59] The importance of insulin resistance affecting these NO mechanisms in MetS is supported by findings of genetic variation at the eNOS locus by haplotype tagging single nucleotide polymorphisms (htSNPs) in patients meeting criteria for the diagnosis of MetS, perhaps indicating a genetic susceptibility for endothelial dysfunction in this context.[66]

Insulin resistance is also linked to endothelial dysfunction through lipotoxicity, which is potentiated by dyslipidemia (particularly, low HDL-C), a component of the MetS cluster. Lipotoxicity can stem from accumulation of harmful lipids in obesity secondary to

metabolic stress from nutrient excess, and the adipokine dysregulation and insulin resistance discussed here.[67] In addition to inhibiting the PI3-K/Akt pathway via inactivation of IRS-1/2, the presence of these harmful free fatty acids stimulates the MAPK pathway and stimulates ROS production, including pro-inflammatory and pro-thrombotic mediator production via NADPH oxidase stimulation.[68–70] Additionally, activation of the MAPK pathway, which is also activated from hyperinsulinemia secondary to insulin resistance, increases ET-1 production in the midst of decreased NO production, creating a balance that is offset between high MAPK pathway and low PI3-K/Akt pathway.[71–72] ET-1 expression by both insulin resistance and free fatty acids is also potentiated by ROS activation of NF-kB.[73] To note, in addition to vasoconstriction via endothelin A (ET-A) receptors on vascular smooth muscle cells, ET-1 induces mitogenic activity that causes proliferation of smooth muscle cells and vessel proteins to promote atherosclerosis.[74–75] With respect to the impact of dyslipidemia potentiating lipotoxicity, low HDL-C in hyperlipidemic patients were shown to have higher levels of VCAM-1 and ICAM-1 contributing to endothelial damage.[76] Similar to hyperinsulinemia, oxidized LDL-C contributes to a reduction in NO production but is mediated by upregulation of arginase I, decreasing L-arginine availability to eNOS.[77] Therefore, the importance of HDL with atherosclerosis, which prevents lipoprotein oxidation, can be appreciated for its protection against both endothelial dysfunction and subsequent atherosclerosis.

Evidence of a Syndrome and Diagnostic Considerations for AVD

As discussed above, MetS is a clinical diagnosis that consists of the clustering of cardiovascular disease factors (ATP III criteria) with debate on whether their cardiovascular risk is collectively greater than the summation of their individual contributions.[78–80] While a paucity of data exists in relation to this gap in knowledge, the current clinical approach is to address each risk factor among the cluster individually.[1] Current diagnostic assessment has yet to attribute a higher risk profile for any AVD with MetS and would be necessary if synergism exists. Nevertheless, as discussed with the Framingham Heart Study, an elevated RBP4 was associated with MetS independent of obesity and may be evidence of a syndrome process in relation to insulin resistance, and likewise a diagnostic possibility deserving further evaluation. Furthermore, in MetS, adiponectin may also offer some clarity despite lower levels of it with adipocyte dysfunction in metabolically healthy obesity.

Contrary to the Framingham study and in support for the diagnostic value of adiponectin in MetS, Hung et al. found that low circulating levels were associated with pro-inflammatory markers, insulin resistance and MetS independent of obesity.[81] Outside of considering adipokine dysregulation and insulin resistance, in a prospective study among those with clinically defined MetS, the individual components of the ATP III criteria were synergistically associated with reduced cholesterol efflux capacity, a mechanism and potential diagnostic marker by which macrophages regulate cholesterol metabolism and homeostasis to prevent cholesterol accumulation.[82] Among the first to show an escalation in risk among the diagnostic cluster of MetS, this study also showed that reduced cholesterol efflux capacity is seen in atherosclerotic plaques across various vascular beds, providing a link between cardiometabolic disease and AVD. With the evidence taken together here, the possibility that MetS is a true syndrome is sufficient to investigate the magnitude and

etiology of possible risk escalation, or synergism, that would be greater than the sum of individual ATP III criteria.

Outside of the context of a syndrome, the adverse adipokine profile seen in metabolically healthy obese subjects of the Framingham included high levels of RBP4, fetuin-A and low levels of adiponectin that may have relevance to assess AVD risk among adipokine dysregulation without a syndrome process. Irrespective of MetS, several pro-inflammatory and pro-thrombotic mediators exist with adipokine dysregulation and insulin resistance (Figures 2 and 3) and require prospective and temporal evaluation for refined diagnostic and prognostic utilization, respectively, with AVD. Likewise, AVD stemming from adipokine dysregulation or insulin resistance, may be better served with adjunctive anti-inflammatory treatment that could complement current anti-thrombotic efforts with AVD. Finally, genetic possibilities may exist that underlie these two atherogenic metabolic processes and are a worthy endeavor diagnostically. For example, a genomic polymorphism has been noted in the adiponectin (AdipoQ) gene (locus on chromosome 3q27) related to dysregulation causing low levels.[83] Additionally, as noted earlier, genetic variation (htSNPs) at the eNOS locus may explain susceptibility to endothelial dysfunction relative to insulin resistance and subsequent atherosclerosis.[66] Likewise, the role of specific microRNAs, which are posttranscriptional regulators, have been shown to be expressed or downregulated during atherogenic processes secondary to adipokine dysregulation, and endothelial dysfunction secondary to insulin resistance, respectively.[84–85]

Conclusion

With the debate of whether MetS is truly a syndrome process with synergism and advanced risk, the hallmark sequelae implicated in the disease of adipokine dysregulation and insulin resistance are significant derangements that also work independently with atherosclerotic vascular disease. The pathophysiology learned from our attempts to understand MetS further, offer diagnostic potential to atherosclerotic vascular disease. Nevertheless, the possibility that the MetS diagnostic cluster accounts for a higher atherogenic risk than the individual ATP III risk factors responsible for adipokine dysregulation and insulin resistance is a warranted endeavor and should be the focus for this ‘syndrome’ in the future.

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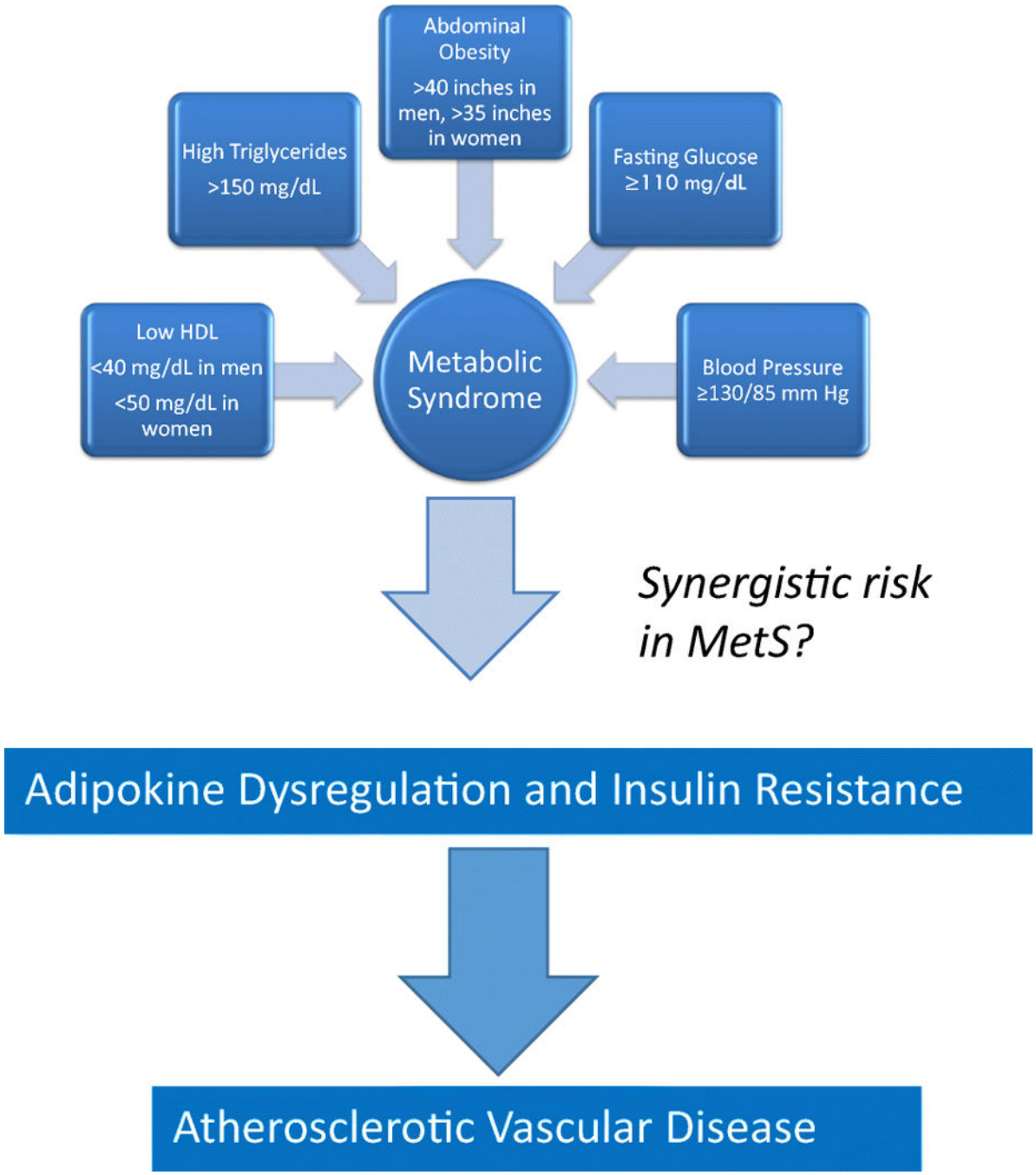

Figure 1:
Schematic diagram showing an association between metabolic syndrome and atherosclerotic vascular disease

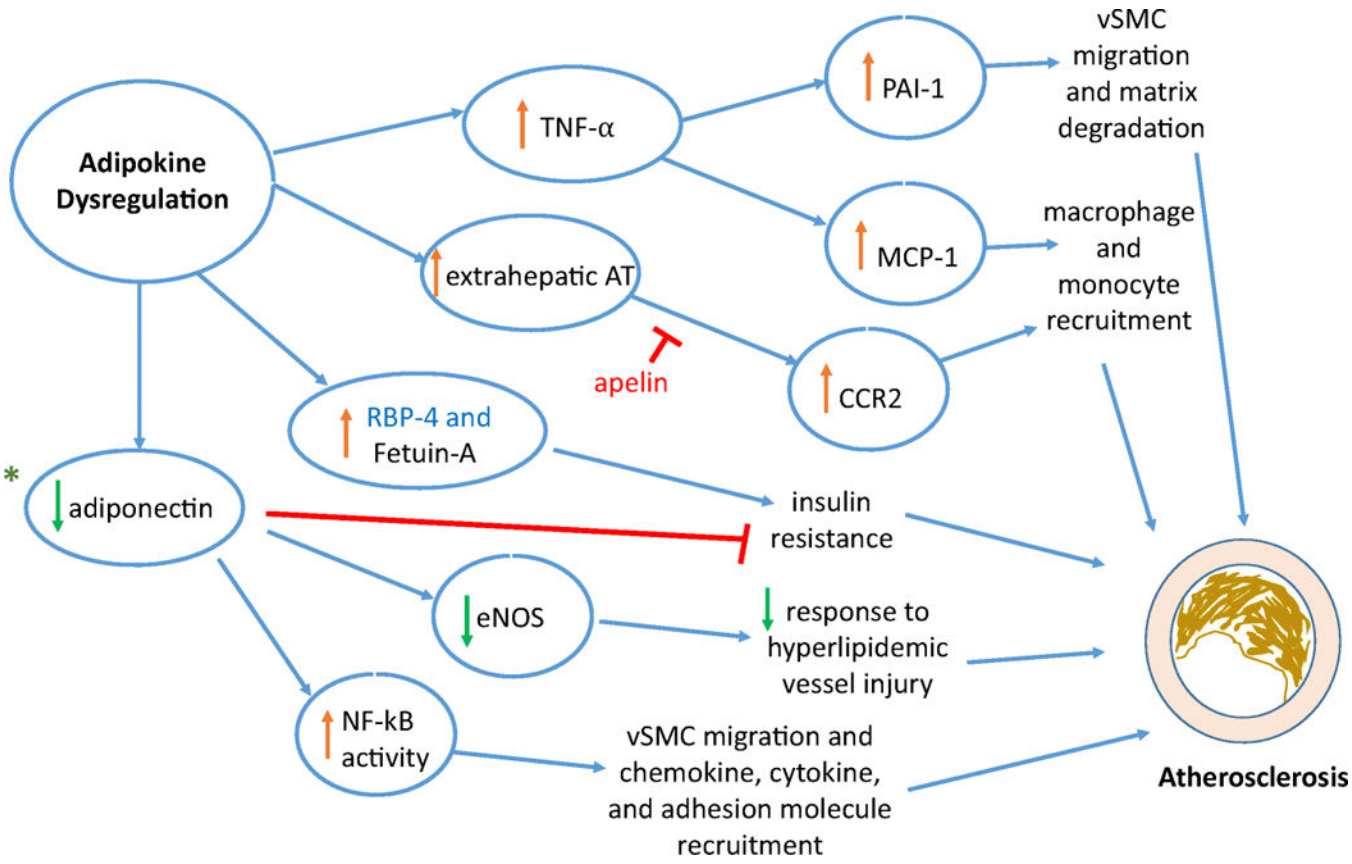

Figure 2:

Mediators involved due to adipokine dysregulation leading to the pathophysiology in the development of atherosclerosis.

Adipokines ➔ tumor necrosis factor – alpha (TNF-α); extrahepatic angiotensin (AT); retinol-binding protein-4 (RBP-4); fetuin-A, adiponectin, plasminogen activator inhibitor-1 (PAI-1); Mediators Impacted ➔ monocyte chemoattractant protein (MCP-1); C-C chemokine receptor type 2 (CCR2) signaling; endothelial nitric oxide synthase (eNOS); nuclear factor-kappa light-chain-enhancer of activated B cells; *Diagnostic targets ➔ genetic predisposition: adiponectin (AdipoQ gene) polymorphisms and specific microRNAs of adipokine dysregulation promoting atherosclerosis; Therapeutic target ➔ apelin; MetS link ➔ RBP-4; vSMC - vascular smooth muscle cells

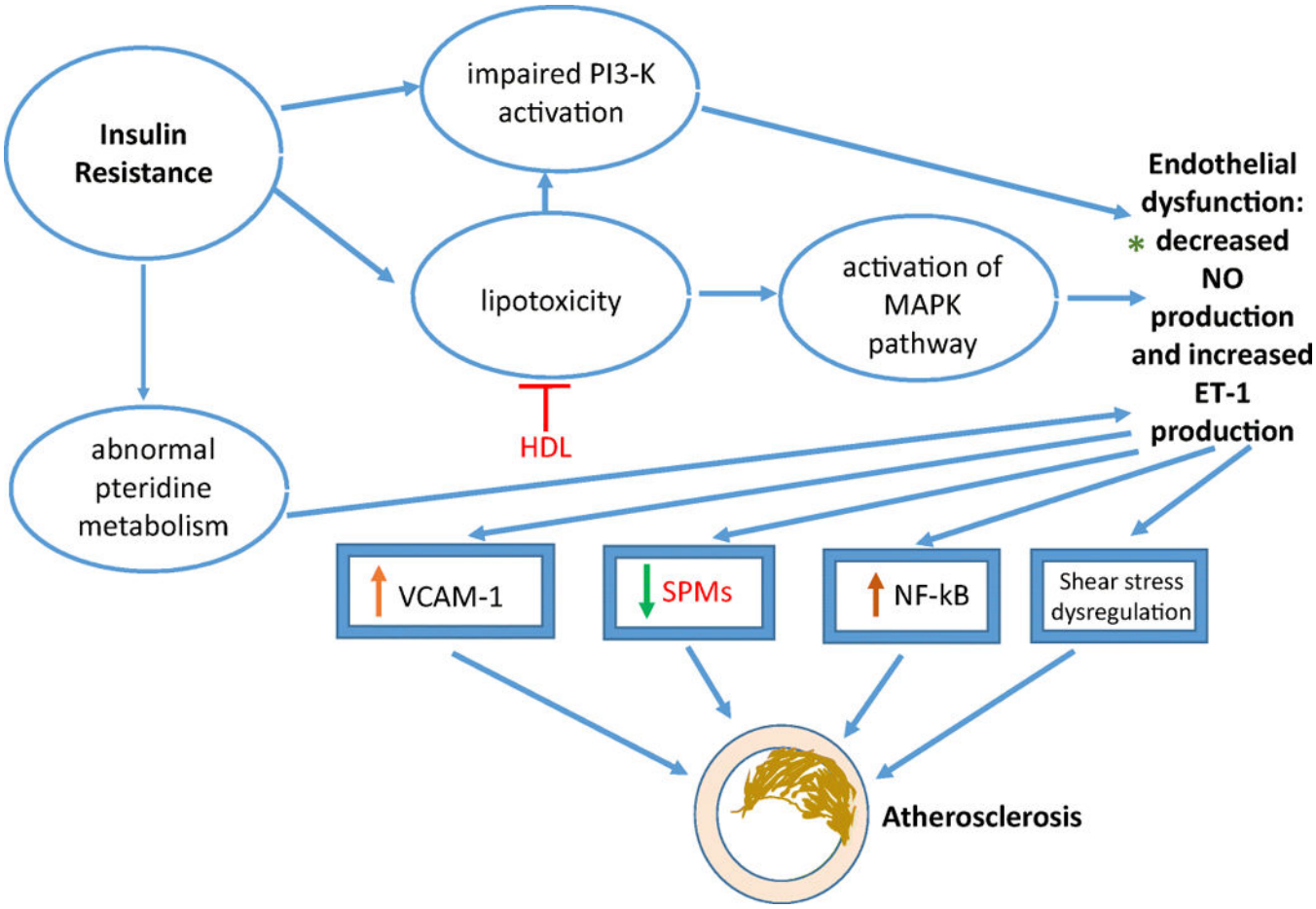

Figure 3: Insulin Resistance and Development of Atherosclerosis

Signaling pathways ➔ phosphatidylinositol 3-kinase (PI3-K); mitogen-activated protein kinase (MAPK); Mediators ➔ nitric oxide (NO); endothelin-1 (ET-1), vascular cell adhesion molecule-1 (VCAM-1), nuclear factor-kappa light-chain-enhancer of activated B cells, specialized pro-resolving mediators (SPMs); *Diagnostic targets ➔ genetic predisposition to atherosclerosis: genetic variation in haplotype tagging single nucleotide polymorphisms (htSNPs) at the eNOS locus & specific microRNAs of insulin resistance promoting atherosclerosis; Therapeutic targets ➔ upregulation of high-density lipoprotein (HDL) to induce anti-oxidative effect and reduce lipotoxicity and SPM delivery to resolve inflammation associated with insulin resistance.

Table 1:

Major Criteria to Define Metabolic Syndromen

Criterion	Characteristics of the criterion
Abdominal obesity (waist circumference)	men >102 cm (40 in.) women >88 cm (35 in.)
Fasting Serum triglycerides	≥150 mg/do OR drug treatment for elevated triglycerides
Fasting Serum HDL cholesterol (HDL-C)	<40 mg/dl in men <50 mg/dl in women OR drug treatment for low HDL-C
Blood pressure	≥130/85 mmHg OR drug treatment for elevated blood pressure
Fasting plasma glucose	≥100 mg/dl OR drug treatment for elevated blood glucose