

Review

Systematic Review of Metabolic Syndrome Biomarkers: A Panel for Early Detection, Management, and Risk Stratification in the West Virginian Population

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Abstract

Introduction: Metabolic syndrome represents a cluster of related metabolic abnormalities, including central obesity, hypertension, dyslipidemia, hyperglycemia, and insulin resistance, with central obesity and insulin resistance in particular recognized as causative factors. These metabolic derangements present significant risk factors for cardiovascular disease, which is commonly recognized as the primary clinical outcome, although other outcomes are possible. Metabolic syndrome is a progressive condition that encompasses a wide array of disorders with specific metabolic abnormalities presenting at different times. These abnormalities can be detected and monitored via serum biomarkers. This review will compile a list of promising biomarkers that are associated with metabolic syndrome and this panel can aid in early detection and management of metabolic syndrome in high risk populations, such as in West Virginia.

Methods: A literature review was conducted using PubMed, Science Direct, and Google Scholar to search for markers related to metabolic syndrome. Biomarkers searched included adipokines (leptin, adiponectin), neuropeptides (ghrelin), pro-inflammatory cytokines (IL-6, TNF- α), anti-inflammatory cytokines (IL-10), markers of antioxidant status (OxLDL, PON-1, uric acid), and prothrombic factors (PAI-1).

Results: According to the literature, the concentrations of pro-inflammatory cytokines (IL-6, TNF- α), markers of pro-oxidant status (OxLDL, uric acid), and prothrombic factors (PAI-1) were elevated in metabolic syndrome. Additionally, leptin concentrations were found to be elevated in metabolic syndrome as well, likely due to leptin resistance. In contrast, concentrations of anti-inflammatory cytokines (IL-10), ghrelin, adiponectin, and antioxidant factors (PON-1) were decreased in metabolic syndrome, and these decreases also correlated with specific disorders within the cluster.

Conclusion: Based on the evidence presented within the literature, the aforementioned biomarkers correlate significantly with metabolic syndrome and could provide a minimally-invasive means for early detection and specific treatment of these disorders. Further research is encouraged to determine the efficacy of applying these biomarkers to diagnosis and treatment in a clinical setting.

Key words: Metabolic syndrome, literature review

Introduction

Metabolic syndrome is a cluster of metabolic abnormalities which confers upon an individual a substantial increase in cardiovascular disease (CVD) risk - approximately twice as high as those without the syndrome. Compared to those without metabolic

syndrome, those with it are at an increased risk of mortality from CVD, coronary heart disease, stroke, vascular dysfunction, and all-cause mortality [1]. While the pathogenesis of metabolic syndrome and its components is not well understood, central obesity

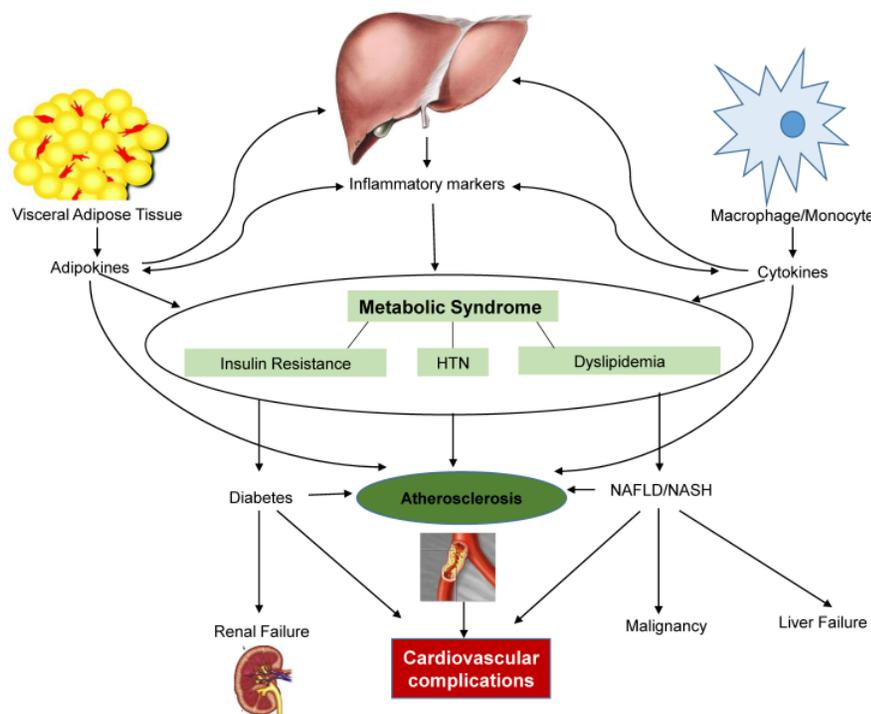


Figure 1: Interaction of adipokines, cytokines, and inflammatory markers that contribute to the development of metabolic syndrome and its complications. HTN-Hypertension, NAFLD/NASH- Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis

and insulin resistance are recognized as causative factors. Several different organizations have outlined diagnostic criteria for metabolic syndrome, which designates values for obesity (waist circumference or BMI), triglyceride levels, HDL (High Density Lipoprotein)

levels, hypertension, hyperglycemia, and sometimes urine albumin or albumin: creatinine ratio (Table 1). Based on AHA criteria, nearly 35% of US adults, and 50% of those older than 60 years old, have metabolic syndrome [2]. Regardless of which criteria are used, the primary concern is early detection of potential CVD complications and early intervention [3, 4].

Though the NCEP ATP III report and WHO have both identified CVD as the primary clinical outcome of metabolic syndrome, most people with metabolic syndrome will have insulin resistance, which results in increased risk for type 2 diabetes (Figure 1). Once diabetes becomes clinically apparent, CVD risk rises sharply. In addition to CVD and type 2 diabetes, individuals with metabolic syndrome are seemingly more susceptible to other conditions, including polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer, such as breast, pancreatic, colorectal, and prostate [5, 6].

Table 1: Diagnostic Criteria for Metabolic Syndrome

	IDF (Obesity + ≥2)	AHA(≥3)	NCEP ATP III (≥3)	WHO(Insulin resistance/Diabetes + ≥2)	EGIR(hyperinsulinemia + ≥2)
Obesity	BMI >30kg/m ² or specific gender and ethnicity waist circumference cutoffs	Waist circumference for males >40in, females>35in	Waist circumference for males >40in, females>35in	Waist/hip ratio>0.9 in males and >0.85 in females or BMI>30kg/m ²	Waist circumference for males ≥94cm, females≥80cm
Elevated Triglycerides	TG≥150mg/dL or treatment of this lipid abnormality	Fasting TG≥150mg/dL or treatment of this lipid abnormality	TG≥150mg/dL or treatment of this lipid abnormality	TG≥150mg/dL	TG ≥177mg/dL
Decreased HDL	HDL <40mg/dL in males and <50mg/dL in females or specific treatment for this lipid abnormality	HDL<40mg/dL in males and <50mg/dL in females or treatment for this lipid abnormality	HDL<40mg/dL in males and <50mg/dL in females or treatment for this lipid abnormality	HDL<35mg/dL in males and <39mg/dL in females	HDL< 39 mg/dL
Hypertension	SBP ≥130 or DBP ≥85 mm Hg or treatment of previously diagnosed hypertension	BP>130/85mm Hg or taking medication for hypertension	SBP ≥130 or DBP ≥85 mm Hg or taking medication for hypertension	≥140/90mm Hg	≥140/90mm Hg or taking medication for hypertension
Hyperglycemia	Fasting plasma glucose >100mg/dL or previously diagnosed type 2 diabetes	Fasting glucose >100mg/dL or taking medicine for high glucose	Fasting glucose >100mg/dL or taking medicine for high glucose	Insulin resistance required	Insulin resistance required(plasma insulin >75 th percentile)
Other				Urine albumin ≥ 20µg/min or Albumin: creatinine ratio ≥ 30mg/g	

IDF- International Diabetes Federation, AHA- American Heart Association, NCEP ATP III- National Cholesterol Education Program-Adult Treatment Panel III, WHO- World Health Organization, EGIR- European Group for the Study of Insulin Resistance, BMI- Body Mass Index, SBP - Systolic Blood pressure, DBP- Diastolic Blood Pressure, BP - Blood Pressure, TG- Triglycerides, HDL-High Density Lipoprotein

Based on "The state of obesity: 2014 report", West Virginia ranks highest in the country for obesity prevalence (35.1%) in the adult population. WV is also highest-ranked for prevalence of hypertension (41%), and ranked second for prevalence of diabetes (13%) in the adult population. Given the extent of disease burden in our state, it can be inferred that West Virginia also has one of the highest prevalences, if not the highest, of metabolic syndrome and subsequent complications, though no epidemiological data is available through a literature search on PubMed. It is imperative to find a way to decrease these complications, and early detection is paramount to this process, yet frequently diagnosis is only possible once complications have already begun.

Research shows that adipocytes produce bioactive substances, known as adipocytokines or adipokines. Accumulation of adipocytes leads to the dysregulated production of adipokines, which contributes to the development of metabolic syndrome [7]. The list of these dysregulated adipokines and cytokines is constantly growing and is a reflection of the heterogeneity of adipose tissue due to the number of resident cell types [8].

The mechanism by which adipose accumulation elucidates dysregulation is not entirely clear at this time, but some suggest that it is at least partly due to systemic oxidative stress brought on by obesity [9]. One proposed mechanism by which obesity produces oxidative stress is mitochondrial and peroxisomal oxidation of fatty acids, which can generate reactive oxygen species (ROS) in oxidation reactions. Malondialdehyde (MDA), a lipid peroxidation end product, is increased in conditions marked by obesity and insulin resistance. It is able to enhance expression of pro-inflammatory cytokines, resulting in systemic stress [10]. In addition to MDA, F₂-isoprostanes (F₂-IsoPs) are also a product of polyunsaturated fatty acid peroxidation. A study has shown that BMI is significantly correlated with the F₂-IsoP concentration. Another marker of oxidative stress is urinary 8-iso prostaglandin F₂ α (8-iso PGF α). It has been shown to be positively correlated with obesity and insulin resistance [11].

For many pathological states, medicine relies on biomarkers to aid in diagnosis and management when overt clinical signs or gross anatomic abnormalities are absent or are not obvious. In addition to this, biomarkers can identify individuals within a population susceptible to disease on the basis of a "genotype" rather than on a reported history. Biomarkers also afford the ability to quantify this susceptibility, allowing for an estimation of disease risk for a population [12].

A panel of metabolic syndrome biomarkers

could provide a relatively easy, minimally-invasive means of identifying those who are at risk for developing metabolic syndrome and subsequent complications. A panel, rather than just individual biomarkers, would be useful since biomarkers can have multiple roles and pathways in which they are involved, so it would be difficult to say that one biomarker alone is sensitive and specific for the diagnosis of metabolic syndrome. Furthermore, many of these biomarkers are interrelated in how they play a role in metabolic syndrome, so correlations between biomarkers would be helpful to assess patients. With this early detection, early intervention is also possible and could be an effective means to diminish the widespread effects this syndrome has on the West Virginian population, as well as on others. A panel could also provide a mechanism to personalize treatment given the etiology differences amongst individuals. While there are numerous articles listing the biomarkers, both established and emerging, this review will compile a panel of the most researched biomarkers and provide evidence of their relation to metabolic syndrome. This panel could provide a way to diagnose, risk stratify, monitor and potentially treat individuals at the molecular level.

Methods

A literature review was performed using PubMed, Science Direct, and Google Scholar from commencement to present and last search was done August 25, 2015. All databases were searched for the following keywords in varying combinations: "biomarkers", "metabolic syndrome", "leptin", "adiponectin", "uric acid", "leptin/adiponectin ratio", "plasminogen activator one", "Interleukin 6 (IL-6)", "Interleukin 10 (IL-10)", "ghrelin", "tumor necrosis factor(TNF α)", "paraoxonase", "oxidized LDL", "weight loss", and "medications".

Results

Leptin

Leptin is an adipokine, which under normal physiological conditions functions to reduce appetite, increase energy expenditure, increase sympathetic activity, facilitate glucose utilization, and improve insulin sensitivity [13]. It is expressed in levels proportionate to adipose mass, and though it is produced mostly by adipocytes, it is also produced by vascular smooth muscle cells, cardiomyocytes, and placenta in pregnant women. The functional leptin receptor is in the hypothalamus where it functions to increase energy expenditure and reduce appetite. The receptor is also found in other organs such as the heart, liver, kidneys, and pancreas; it is also present in the smooth

muscle and endothelium of heart, brain vasculature, and myometrium [14]. Given the wide range of targets for leptin based on receptor locations, the effects of it are also widespread. Leptin has a functional receptor, Ob-Rb, in the myocardium, and studies have shown a direct link between leptin and myocardial structural remodeling [15]. There is controversy as to whether leptin causes or protects from left ventricular hypertrophy (LVH) as research has shown mixed results, though more suggest it contributes to LVH [14, 16]. Independent of conventional risk factors, studies have shown that leptin can predict myocardial infarction [17]. Leptin also affects vascular structure by promoting hypertension, angiogenesis, and atherosclerosis [14].

Leptin's role as a biomarker for metabolic syndrome has been researched in different populations. Regardless of which demographic studied, elevated leptin levels are associated with metabolic syndrome. This is not surprising given that elevated leptin is associated with obesity, insulin resistance, myocardial infarction, and congestive heart failure [14]. Yoshinaga et al found that leptin was the most sensitive marker for predicting metabolic syndrome (and cardiovascular risk) in elementary school children [18]. Lee et al found that leptin was elevated in postmenopausal women with metabolic syndrome. They found a positive correlation with leptin and abdominal obesity (one of the components of metabolic syndrome), and with the number of components of metabolic syndrome present [19]. A study of a Lebanese population, which focused on nondiabetic males over fifty years old, also found elevated leptin levels associated with metabolic syndrome. This study found that leptin was strongly correlated with waist size, but was only weakly correlated with lipid profile, which disappeared with BMI adjustment [20]. Similar findings of elevated leptin associated with metabolic syndrome, independent of BMI, were found in a Korean population. In this study by Yun et al, serum leptin levels increased as the components of metabolic syndrome increased, regardless of obese and nonobese weight status, implying that reduction of leptin levels may be protective, regardless of weight loss [21]. Contrary to this, Martins et al, found a direct positive association between leptin and obesity, hyperinsulinemia and insulin resistance, but was only weakly related to other components of metabolic syndrome [22]. Though there is some dissension in the literature about whether leptin is associated with metabolic syndrome independent of BMI, the general consensus is that it is elevated in metabolic syndrome in children, the elderly, females, and males, and therefore can serve as an effective biomarker on a screening panel.

Adiponectin

Adiponectin, like leptin, is an adipose-derived plasma protein with widespread effects. However, unlike leptin, it is secreted exclusively from adipocytes [23]. The different forms of adiponectin include low molecular weight trimer, middle molecular weight hexamer, and high molecular weight (HMW). The HMW form is believed by many to be the more active form and has the most favorable metabolic effects on insulin sensitization and protection against diabetes [14, 23, 24]. Adiponectin has many functions, including anti-atherogenesis, insulin sensitization, lipid oxidation enhancement, and vasodilatation. Therefore, it stands to reason that it is related to metabolic syndrome given its impact on all of these components. It suppresses almost all processes involved in atherosclerotic vascular change: the expression of adhesion molecules in vascular endothelial cells, adhesion of monocytes to endothelial cells (via TNF- α inhibition), vascular smooth muscle cell proliferation and migration, and foam cell formation (via oxidized LDL (OxLDL) inhibition) [25]. It has insulin-sensitizing activities, with high levels exerting a protective effect against type 2 diabetes in diabetes-prone individuals [7] and low levels being an independent risk factor for future development of type 2 diabetes [26]. Levels of adiponectin are low in subjects with essential hypertension and in the obese, but adiponectin levels can be increased with weight loss [7, 27].

A study of Japanese adults by Ryo et al showed that adiponectin levels were negatively correlated with waist circumference, visceral fat, serum triglycerides, fasting plasma glucose, fasting plasma insulin, and systolic and diastolic blood pressure in males and females, and positively correlated with HDL. As the mean number of metabolic syndrome components increased, plasma adiponectin levels decreased. They found that men had lower levels of adiponectin than women, which is interesting since it may be part of the reason why women have a lower risk of coronary artery disease [7]. Gannage et al found adiponectin to be inversely correlated with metabolic syndrome, independent of BMI as other studies have also shown in the past [20, 28]. Santaneimi et al studied a Finnish population and found decreasing adiponectin levels correlated with an increasing number of components of metabolic syndrome in both sexes, and this was once again independent of BMI [27]. Overall, the literature shows that adiponectin is inversely related to metabolic syndrome and the number of components present. However, many believe HMW adiponectin to be the more active form and Falahi et al suggest that HMW adiponectin may even be the most reliable biomarker for metabolic syndrome diagnosis [29].

Hara et al found that the ratio of HMW adiponectin to plasma adiponectin was an even better predictor of insulin resistance and metabolic syndrome [30]. Therefore, adiponectin, and preferably HMW adiponectin, should be considered on a panel of biomarkers for metabolic syndrome diagnosis.

Leptin: Adiponectin Ratio

Other studies have determined that the leptin: adiponectin ratio (LAR) is more beneficial than either alone. Falahi et al showed that a high LAR is a better biomarker than leptin or adiponectin alone for the diagnosis of metabolic syndrome [29]. A study of Japanese patients found that LAR was significantly and positively associated with the number of components of metabolic syndrome present, and the ratio was independently associated with each component of metabolic syndrome [31]. However there may be differences to this between males and females. Cicero et al found the LAR to be strongly associated with metabolic syndrome, especially in males. The association was weaker in females since they had more elevated adiponectin levels, which is thought to be protective against metabolic syndrome [32]. Others postulate that the ratio difference between males and females is due to the difference in glucose and lipid metabolism [31]. One limiting factor with using just adiponectin or leptin is that the difference between adiponectin and leptin tends to be small in the fasting vs postprandial state. Therefore, one of the benefits of using the LAR is that it has the potential to assess insulin sensitivity and metabolic syndrome in the non-fasting state [33].

Ghrelin

Ghrelin is a neuroendocrine hormone secreted primarily by the stomach that stimulates appetite directly via activation of the GH secretagogue receptor 1a (GHSR-1a) in the hypothalamus, and indirectly by increasing expression of orexigenic peptides, such as neuropeptide Y (NPY) [34, 35]. It may also be protective of vasculature by antagonizing the effects of vasoconstrictors, such as endothelin 1, and promoting the effects of vasodilators, such as nitric oxide (NO) [36]. Furthermore, it can help to promote lipolysis via stimulation of hypothalamic AMP-activated protein kinase (AMPK) [35]. Research into the vasoprotective and lipolytic properties of ghrelin is emerging and presents two pathways by which ghrelin can exert a protective effect against metabolic syndrome.

Metabolic syndrome is associated with lower levels of ghrelin, and progressively lower ghrelin levels are associated with increasing metabolic syndrome severity. Ghrelin levels decrease with increasing number of metabolic syndrome derangements [37-40].

This trend is significant even after adjusting for age and sex, though ghrelin levels have been shown to be higher in females than males [37, 38]. Low ghrelin levels have been associated with the components of metabolic syndrome including obesity, insulin resistance, and hypertension [41-43]. However the association between low ghrelin and metabolic syndrome is likely primarily explained by the relationship to obesity as obese patients with metabolic syndrome have lower ghrelin levels than nonobese counterparts [44]. Furthermore, amongst obese patients, ghrelin levels are lower in insulin resistant patients compared to insulin sensitive obese patients [45]. Plasma ghrelin levels are also decreased in the healthy offspring of type 2 diabetes patients suggesting a genetic component to ghrelin regulation [37]. Ghrelin is implicated in endothelial function by preventing proatherogenic changes and improving vasodilation [37]. Tesouro et al assessed vascular function by measuring forearm blood flow in metabolic syndrome and control patients. They showed that exogenous ghrelin significantly reduced the vasoconstrictor effects of endothelin 1 and enhanced the vasodilator effects of NO in metabolic syndrome patients, but did not have a significant effect on vascular tone in control patients [36]. Given ghrelin's relation to each of the components of metabolic syndrome, to metabolic syndrome itself, and the potential to note abnormal levels in healthy individuals with genetic predispositions, it would be an effective biomarker for metabolic syndrome.

Plasminogen Activator Inhibitor – I

Plasminogen Activator Inhibitor-1 (PAI-1) is the primary of four serine peptidase inhibitors that functions to modulate extracellular matrix remodeling and fibrinolysis. It binds to and deactivates tissue plasminogens (tissue type plasminogen activator (tPA), urokinase plasminogen activator (uPA)). tPA is thought to be responsible for intravascular plasminogen activation, with fibrin regulating its activity, and uPA is responsible for plasminogen activation on migrating cells, with the uPA receptor regulating its activity on different cells. Thus, PAI-1 can inhibit intravascular fibrinolysis and cell-associated proteolysis [46].

Under physiologic conditions, PAI-1 is secreted into the circulation or extracellular space by endothelial cells, adipocytes, vascular smooth muscle cells, platelets, or hepatocytes. Under pathologic conditions however, PAI-1 is induced by many pro-inflammatory and pro-oxidant factors. For example, when TNF- α , transforming growth factor beta (TGF- β), angiotensin II, glucocorticoids, and insulin are elevated, adipocytes are stimulated to increase PAI-1 levels. Hypoxia

and ROS also increase PAI-1 levels. Elevated levels of PAI-1 consequently effect vasculature, inflammatory signaling, adiposity, and insulin resistance [47].

Aberrant PAI-1 levels are associated with several pathological diseases. For example, high levels are positively correlated with thrombotic vascular conditions such as myocardial infarction and deep vein thrombosis. This is thought to be related to the inhibition of fibrin degradation and vessel wall remodeling. It is thought to be a strong risk factor for coronary artery disease and some suggest it can be used as an independent risk factor for cardiovascular risk [48, 49]. It has also been implicated in cancer angiogenesis and metastasis, wound healing, bacterial infections, rheumatoid arthritis, and chronic kidney disease [50].

The link between PAI-1 and metabolic syndrome has been long established with elevated levels being strongly correlated such that the more severe the metabolic syndrome, the higher the PAI-1 [51-53]. Kraja et al showed that PAI-1 was strongly associated with the components of metabolic syndrome, including BMI, triglycerides and insulin resistance [47]. Interestingly, several groups have found that PAI-1 levels are not associated with dyslipidemia but rather with the distribution phenotype of adipocytes: visceral adipose tissue primarily and ectopic fat in the liver [54, 55]. Given this, some suggest PAI-1 can serve as a biomarker for ectopic fat storage. Like several of the other metabolic syndrome biomarkers, differences between the sexes have been noted, with the relationship being stronger in males than females [55]. PAI-1 levels decrease with calorie restriction, weight loss, decrease in body fat, and when insulin resistance improves [46, 56]. Treatment with insulin-sensitizing drugs decreases PAI-1 in patients with diabetes and to some extent in otherwise healthy obese individuals [57].

Uric Acid

Uric acid is an endogenously produced terminal degradation product of purine catabolism, formed by the liver and excreted by the kidneys primarily and intestines secondarily. Uric acid has antioxidant capacities extracellularly and can be responsible for 2/3 of the total plasma antioxidant capacity, where it chelates metals and scavenges oxygen radicals. However, intracellularly, it has pro-inflammatory and pro-oxidant activity. It has been shown that uric acid is a circulating marker for oxidative damage in conditions like ischemic liver, atherosclerosis, diabetes, and chronic heart failure [58]. As a pro-oxidant, under ischemic conditions or as a result of tissue damage, uric acid oxidizes lipids, which results in inflammation that disrupts reverse cholesterol transport [59]. It also decreases the availability of nitric oxide, which

results in less vasodilation and more reactive oxygen species (ROS). This, coupled with its ability to stimulate monocytes to produce TNF- α , creates a pro-inflammatory state found in metabolic syndrome. Though its role in pathological diseases is not completely understood, uric acid likely causes systemic inflammation [58].

Hyperuricemia is a well-known risk factor for atherosclerotic events like myocardial infarction and stroke, and is associated with other cardiovascular risk factors like hypertension and dyslipidemia. Ishizaka et al also found a positive correlation between uric acid and BMI, blood pressure, and triglycerides, and a negative correlation with HDL-C [60]. Silva et al shows that uric acid levels are significantly elevated in males with abdominal obesity and females with abdominal obesity, low HDL-C, and hypertension [61]. It is also suggested that hyperuricemia is a marker of insulin resistance, as some studies have shown that decreasing insulin resistance by diet or medications decreases uric acid levels [62-64]. Among dietary causes of hyperuricemia, excess consumption of fructose via added sucrose or high-fructose corn syrup is of particular interest, as this dietary component has also been implicated in metabolic syndrome. According to Khitan and Kim, fructose metabolism is initiated by an enzyme called ketohexokinase (KHK), also known as fructokinase. This ATP-dependent step in fructose metabolism lacks a negative feedback mechanism, so in the event of excessive fructose consumption, ATP is rapidly depleted and many of the dephosphorylated adenosine compounds are catabolized, resulting in increased uric acid [65]. Johnson et al demonstrated a link between fructose-induced hyperuricemia and an increased incidence of metabolic syndrome and some of its features, including obesity, hypertension, and insulin resistance [66].

Given the relation of uric acid and all the components of metabolic syndrome, it is expected that uric acid would be elevated for metabolic syndrome as a whole as well. Ishizaka et al investigated the relationship between uric acid and metabolic syndrome and found there to be a graded increase in the prevalence of metabolic syndrome with increasing uric acid in both sexes, though there are differences in the levels between males and females [60]. Levels of uric acid increase with age: in women of childbearing age, levels are lower, but increase to similar levels as males when postmenopausal [67]. Several studies have shown that uric acid levels are significantly elevated in individuals with metabolic syndrome, increases with the number of components of the condition, and is an indicator of worse cardiovascular risk profile [61, 68, 69]. It is estimated that individuals with a high uric

acid have an odds ratio of 1.6-fold higher for developing metabolic syndrome [70]. The close relationship between uric acid and the presence of metabolic syndrome has been demonstrated in children, adolescents, and adults [71].

Through a search of the published literature to date, uric acid appears to be the only metabolic syndrome biomarker studied in the West Virginian population. Soukup et al studied salivary uric acid as a biomarker for metabolic syndrome and found the relationship to metabolic syndrome and each of its components similar to that of serum uric acid [72]. Similar to other studies, Soukup et al noted a stronger association between uric acid levels and metabolic syndrome in females than in males [72-74]. This is a noninvasive and cost-effective method to diagnose and monitor metabolic syndrome and its components in rural locations, like West Virginia, where health care capabilities are limited.

Interleukin-6

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that plays a role in the natural inflammatory response. It is often secreted by M1 macrophages as part of the normal inflammatory response against infection and injury [75]. In metabolic syndrome, adipocyte dysfunction is frequently present and is associated with an increase in M1 macrophage population within adipose tissue. This can result in increased secretion of IL-6 and other pro-inflammatory cytokines from adipose tissue. These pro-inflammatory cytokines can then act through a number of cell signaling pathways, including mTOR and Protein Kinase C (PKC) to induce insulin resistance. Through its inflammatory properties it has been implicated in the endothelial cell damage within blood vessels that leads to vascular dysfunction and atherosclerosis. Furthermore, IL-6 can cause aberrant insulin receptor activation, resulting in abnormal insulin signaling cascades, abnormal insulin action, and abnormal glucose metabolism [75].

Studies have shown that elevated levels of IL-6 are associated with metabolic syndrome and increasing levels are associated with more severe metabolic syndrome (assessed by hypertriglyceridemia, hypertension, and fasting glucose levels) [76-78]. Similar to other biomarkers, IL-6 is also associated with each of the components of metabolic syndrome. In a study on postmenopausal women, elevated IL-6 was also associated with abdominal obesity, low HDL, and high triglycerides [77]. Indulekha et al found elevated IL-6 was associated with insulin resistance [78]. In vivo animal studies have shown the effect of IL-6 on insulin signaling: the administration of IL-6 to mice resulted in impaired insulin signaling in muscle and liver tissue, leading to hyperglycemia and insulin

resistance [79].

IL-6's close association with metabolic syndrome and each of its components suggests that it is an important factor in the progression of metabolic syndrome and would be a good addition to a biomarker panel.

Tumor Necrosis Factor-Alpha

Tumor Necrosis Factor-Alpha (TNF- α) is a pro-inflammatory cytokine that is secreted by visceral adipose tissue, a common characteristic of metabolic syndrome [80]. Because metabolic syndrome is often characterized by adipocyte dysregulation, and these dysregulated adipocytes tend to secrete TNF- α , IL-6, and other pro-inflammatory adipokines at higher levels, the central obesity often encountered in metabolic syndrome could be a risk factor for elevated TNF- α levels [75]. Furthermore, elevated TNF- α levels are associated with insulin resistance via its aberrant activation of the mTOR and PKC signaling pathways [75]. Its contribution to the various characteristics of metabolic syndrome suggest that TNF- α may be a significant contributor to the development and progression of its associated disease processes.

In a study of middle-aged adults with metabolic syndrome, elevated levels of TNF- α and other pro-inflammatory cytokines were associated with insulin resistance and hypertriglyceridemia. The TNF- α , IL-6, and leptin levels in these patients were higher than those levels in the control group, indicating that these cytokines directly correlated with metabolic syndrome [81]. It was hypothesized by Balasoiu et al that early detection of a patient's inflammatory status, including TNF- α and IL-6, could be useful in monitoring and early intervention for metabolic syndrome and its comorbidities [81]. In another study of metabolic syndrome patients with coronary artery disease (CAD), TNF- α levels were found to be significantly higher than the controls [82]. Indulekha et al also found elevated TNF- α levels to be significantly correlated with the presence of metabolic syndrome, and more so in those with insulin resistance [78]. Musialik et al demonstrated elevated levels of soluble TNF- α receptor (sTNF α -R), which is associated with increased TNF- α activity, in patients with metabolic syndrome with hypertension [80]. Because it exerts such widespread systemic effects, TNF- α may contribute to the various disease processes associated with metabolic syndrome.

Interleukin-10

Interleukin-10 (IL-10) is a predominantly anti-inflammatory cytokine that plays a role in modulating systemic inflammation. Secreted by monocytes or M2 macrophages, one of its functions is to help

promote normal tissue remodeling following an inflammatory response [75]. One of the methods by which IL-10 moderates the inflammatory response is by inhibiting NADPH oxidase, and therefore the oxidative stress resulting from this enzyme. This has been associated with aberrant insulin receptor substrate (IRS) activation and impaired insulin signaling. Furthermore, the insulin signaling pathway can be dysregulated by abnormal levels of the pro-inflammatory cytokines IL-6 and TNF- α . IL-10 can restore normal insulin signaling by inhibiting NADPH oxidase-induced oxidative stress or by antagonizing the actions of IL-6 and TNF- α [75, 79].

Regarding the role IL-10 plays in insulin signaling, a cross-sectional population study of elderly adults demonstrated that low levels of IL-10 are associated with insulin resistance and type 2 diabetes. Furthermore, the study found that IL-10 levels inversely correlated with levels of total cholesterol, LDL, triglycerides, blood glucose and hemoglobin A1c, and positively correlated with HDL levels [83]. Additionally, in a study on mice treated with IL-6 to induce insulin resistance, *in vivo* administration of IL-10 demonstrated protection from the impaired insulin signaling that resulted from IL-6 administration, thereby restoring insulin sensitivity and normal glucose metabolism in liver and muscle tissue [79]. Because it antagonizes the pro-inflammatory actions of IL-6 and TNF- α , which are both associated with metabolic syndrome and its comorbidities, IL-10 appears to exert a protective effect against increases in these cytokines.

The significance of IL-10 in relation to metabolic syndrome as a whole, rather than its components, however, is a little more complicated. A study of obese children, found IL-10 levels to be elevated in metabolic syndrome, even after BMI was taken into account. Calcaterra et al proposed the elevated levels to be due to the first phase of a complex mechanism in the development of metabolic syndrome in children [84]. Esposito et al studied obese and nonobese women and found IL-10 to be elevated in obese women compared to nonobese women but IL-10 levels were significantly lower in both obese and nonobese women with metabolic syndrome [85]. Others have also shown IL-10 levels to be significantly decreased in those with metabolic syndrome in both males and females [86, 87]. Some have shown that IL-10 levels are significantly correlated with other cytokines like IL-6 and TNF- α . Adiponectin is correlated with IL-10 in patients with metabolic syndrome and not the general population [88]. This suggests that if both IL-10 and adiponectin are low, the risk of metabolic syndrome is likely greater. The use of multiple biomarkers in a panel would likely increase the

sensitivity and specificity.

Oxidized LDL

Oxidized LDL (OxLDL) is a product of lipid oxidation and can serve as a marker of oxidative stress. Lipid oxidation contributes to the generation of reactive oxygen species (ROS). These products form components of OxLDL. Lipid oxidation products, ROS, and OxLDL in low concentrations can serve as signaling compounds for pathways of cellular antioxidants, including Heme Oxygenase (HO-1) and glutathione. However, if the antioxidant capacity of the cell is dysfunctional, as is often seen in metabolic syndrome, then these compounds contribute to an oxidative cascade that eventually leads to cell damage and apoptosis [89]. This widespread cell damage and death can contribute to the vascular dysfunction commonly seen in metabolic syndrome, while the dysfunctional OxLDL can further contribute to dyslipidemia, presenting a risk factor for cardiovascular diseases, which are common comorbidities associated with metabolic syndrome. OxLDL contributes to atherosclerosis by invading and damaging the blood vessel endothelium [90]. In addition to cardiovascular disease, elevated levels of OxLDL in adults are associated with obesity and insulin resistance, two common components of metabolic syndrome [91].

Studies have shown that levels of OxLDL are significantly elevated in metabolic syndrome patients and these elevated levels are further associated with reduced arterial elasticity, a risk factor for the development of CAD [90, 92]. Other studies on children associated elevated levels of OxLDL with increased adiposity and insulin resistance. This study suggested that oxidative stress, measured by OxLDL levels, could be a contributing factor to insulin resistance, and that these changes can present early in life [91]. Additionally, a longitudinal study of young adults measured at baseline, 15 years later, and 20 years later demonstrated a significant positive correlation between OxLDL levels and the incidence of metabolic syndrome that arose between the 15-year and 20-year follow-ups. The study also associated elevated OxLDL levels with central obesity, hyperglycemia, and hypertriglyceridemia, all of which are components of metabolic syndrome [93]. The literature suggests that OxLDL serves not only as a promising biomarker for metabolic syndrome detection, but a plausible mechanism by which the components of metabolic syndrome develop and progress.

Paraoxonase

Paraoxonase-1 (PON-1) is a multipurpose anti-toxic and antioxidant enzyme and is believed to contribute to the antioxidant and anti-inflammatory

properties of HDL [94, 95]. In particular, it can reduce lipid peroxidation and protect LDL and tissue from oxidative stress [96]. Levels of PON-1 activity correlate with systemic antitoxic and antioxidant capacity, whereas oxidative stress and lipid peroxidation are associated with the onset and progression of metabolic syndrome and some of its comorbidities, particularly vascular dysfunction (resulting from OxLDL) [90]. In low concentrations, OxLDL and ROS serve as signaling compounds in cellular antioxidant pathways, which serve to improve cellular protection mechanisms in the face of oxidative stress. However, if these antioxidant pathways are overwhelmed from excessive oxidative stress, the oxidative cascade can progress to cell damage and death, resulting in tissue damage, particularly in vascular endothelial tissue [89]. Because of its antioxidant properties, PON-1 may play a role in managing the normal oxidative signaling pathway, and it could serve as a useful biomarker in assessing antioxidant capacity, and by extension, the propensity for systemic inflammation and vascular dysfunction.

In a study of lean, overweight and obese adolescents, decreased levels of PON-1 were associated with central obesity and metabolic syndrome. Additionally, lower levels of PON-1 were associated with hypertension, hypertriglyceridemia, insulin resistance, impaired glucose tolerance, and increased oxidative stress [94]. Another study of women with and without metabolic syndrome showed a negative correlation between PON-1 levels and the presence of CAD in metabolic syndrome patients [96]. CAD is a significant comorbidity in metabolic syndrome, and lower levels of PON-1 could be suggestive of a diminished effectiveness of HDL to attenuate CAD development and progression. Martinelli et al also found that decreased PON-1 levels were associated with metabolic syndrome, with an inverse correlation between PON-1 levels and the severity of metabolic syndrome and its comorbidities [95]. The literature suggests that PON-1, via its antioxidant properties, could play an important role in attenuating the components of metabolic syndrome that arise and progress as a result of oxidative stress.

Discussion

This paper is an attempt to compile the existing literature of biomarkers with the most substantial evidence of their relationships to metabolic syndrome. Obesity has been classified as a disease state, and this is especially true in the state of West Virginia, where one of the larger cities, Huntington, was listed in a recent CDC report as the most obese in the nation, in the most obese developed country based on average BMI. Thus, a panel of biomarkers that could be used

clinically to help predict and establish metabolic syndrome in individuals would be of immense value, not only in treating those that already have the syndrome, but in decreasing the overall prevalence of the disease in the general population. While there have been a number of studies looking at various cytokines and adipokines thought to act as biomarkers for the syndrome, a panel that can be used in clinical practice does not exist. Some have been shown to have greater potential than others, but no single biomarker has been shown to be indicative of metabolic syndrome alone.

Metabolic syndrome is a multifactorial condition that stems from obesity as the causative factor, though the exact mechanism is yet to be determined. Many suggest that oxidative stress, the hallmark of obesity, is linked to a chronic low-grade inflammation. The induced systemic oxidative stress is thought to be at least partly responsible for the dysregulated secretion of adipokines that contributes to metabolic syndrome [9]. Hypertrophied adipocytes generate high levels of ROS which impacts signaling and neighboring perivascular endothelium or resident immune cells [97]. This is compounded by ROS produced from the resultant metabolic derangements such as hyperglycemia and dyslipidemia. Overall, systemic oxidative stress promotes inflammation, results in endothelial dysfunction and altered lipid metabolism, and affects insulin sensitivity (Figure 2).

Leptin, LAR, PAI-1, uric acid, IL-6, TNF- α , and OxLDL have all been shown to be elevated in metabolic syndrome, across different populations and generally are correlated with the number of components of metabolic syndrome present. On the other hand, adiponectin, ghrelin, IL-10, and PON-1 have all been shown to be decreased in metabolic syndrome (Table 2). Some ratios, such as HMW- adiponectin: adiponectin and LAR are better predictors than any alone. To date, there is no established panel to test for metabolic syndrome, but this review has compiled a panel of the best candidates.

Furthermore, utilizing the panel as a means of customizing treatment and follow up may be possible given that associations have been shown between each of the biomarkers and lifestyle modifications and medications. Though it is difficult to say whether there is a true causal relationship between medications and alterations of the biomarker levels, these associations can at least guide clinicians (Table 2). Weight loss, which is already known as a treatment for metabolic syndrome, has been shown to result in levels of all the biomarkers normalizing. Metformin, ACEI, and statins have shown similar effects, although data for every single biomarker is not available for each of these drugs/drug classes.

The potential for using multiple biomarkers for diagnosis and early detection, and subsequent customization of treatment and risk management, is a blossoming field with much room for research. Despite there being many studies on individual biomarkers, there is a void in research on the implications of multiple biomarkers being abnormal. Creat-

ing such a panel could provide a relatively easy and minimally-invasive way to detect metabolic syndrome and possibly indicate the severity, depending on the combination of aberrations. Such a panel would be highly useful in locations where metabolic syndrome poses a significant burden, such as West Virginia.

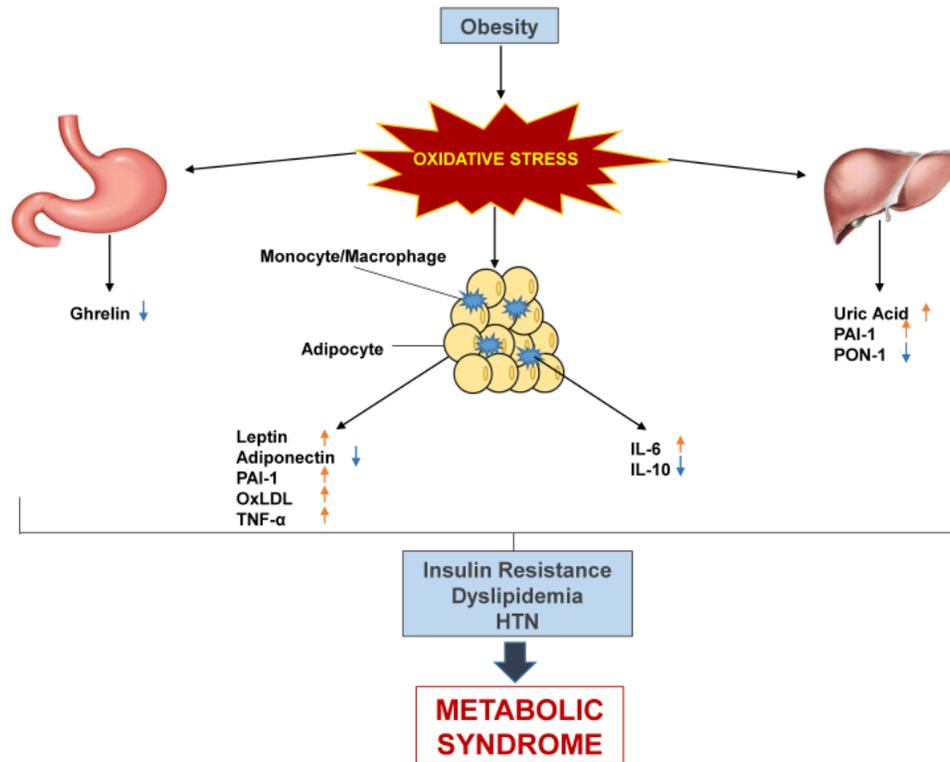


Figure 2: Schematic representation of panel of biomarkers in metabolic syndrome.

Table 2: Biomarker levels in metabolic syndrome and interventions. ACEI- Angiotensin converting enzyme inhibitor; IFN β - Interferon- β

Biomarker	Source	Metabolic Syndrome	Interventions shown to "normalize" levels				
			Lifestyle Modification	Antihypertensive	Diabetic	Lipid Lowering	Other
Leptin	Adipocytes Cardiomyocyte Vascular Smooth Muscle	↑	Weight loss [98]	1. Hydralazine [99] 2. Valsartan[100] 3. Ramipril [98] 4. Candesartan [98] 5. Amlodipine[98] 6. Efonidipine [101] 7. pindolol [102] 8. Bunazosin [103] 9. Methyldopa [99]	Metformin [104]		Bromocriptine [105]
Adiponectin	Adipocytes	↓	Weight loss [106]	Valsartan [107]	1. Metformin [108] 2. Sitagliptin [109] 3. Pioglitazone [110] 4. Troglitazone [111] 5. Rosiglitazone [112] 6. Glimeperide [113]	Atorvastatin (increases HMW adiponectin) [114]	
Ghrelin	Stomach	↓	Weight loss [115]	Valsartan [116]	1. Rosiglitazone [117] 2. Metformin [117]		1.Flutamide [118] 2. Estrogen therapy [119]
PAI-1	Adipocytes Hepatocytes Smooth muscle cells, Platelets	↑	Weight loss [56]	1. Imidapril [120] 2. Candesartan (cannot sustain decreased PAI >4 weeks) [120]	1. Metformin [121] 2. Troglitazone [57]	Statins [122]	Sibutramine [121]
Uric Acid	Liver	↑	Weight loss [123]	1. Losartan [124]	1. Metformin [125]	1.Atorvastatin [126]	1.Sibutramine [125]

Biomarker	Source	Metabolic Syndrome	Interventions shown to “normalize” levels				
			Lifestyle Modification	Antihypertensive	Diabetic	Lipid Lowering	Other
				2. Calcium Channel Blockers [124] 3. ACEI [125]	2.Troglitazone [125]	2.Simvastatin [125] 3.Fenofibrate [125]	2. Orlistat [125]
IL-6	M1 macrophage	↑	Weight loss[127]	1.ACEI [128] 2.Olmesartan [129]	Metformin [130]	1.Atorvastatin [131] 2.Pravastatin [132] 3.Simvastatin [133]	1.Hydrocortisone [134] 2.Celecoxib [135]
TNFα	Visceral Adipocytes, M1 macrophages	↑	Weight loss [127]	Olmesrtan[129]	Metformin [130]	1.Atorvastatin [131] 2.Pravastatin [132]	1.Orlistat [127] 2.Hydrocortisone [134]
IL-10	Monocytes, M2 macrophage	↓	Weight loss[136]		Metformin [130]	Statins [137]	1.Triamcinolone [138] 2.Montelukast [138] 3.IFNβ [139] 4.Beta 1-3 Glucan [140]
OxLDL	Adipocytes	↑	Weight loss [141] Vegan Diet [142]	Fosinopril [143]		1.Statins [144] 2.Ezetimibe [145]	Celecoxib [146]
PON-1	Liver	↓	Weightloss**(decreases pon1) [141]	Eplerenone [147])	1.Rosiglitazone [148] 2.Sulfonueras[149]	1.Fibrates [150] 2.Statins ([151]) 3. Probuco [152] 4.Ezetimibe [145]	

Conclusion

Metabolic syndrome is a condition with genetic and acquired etiologies that results in CVD complications in populations across the world, but especially in the West Virginian population given the rates of obesity, hypertension, and diabetes. Creating a panel of biomarkers with a known and predictable association with metabolic syndrome can provide a means to detect those at risk and intervene as needed. This could significantly decrease the burden complications impose on patients and the healthcare system.

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Competing Interests

The authors have declared that no competing interest exists.

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