Metabolic syndrome, peripheral vascular disease and coronary artery disease: A concise review

Thomas F Whayne Jr MD PhD FICA

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Metabolic syndrome has a very strong association with both forms of cardiovascular (CV) disease – coronary artery disease and peripheral vascular disease. There is also a marked interrelationship between the two forms of CV disease. When one form of CV disease is present, the other should be strongly suspected and the possible occurrence of associated vascular events should be clinically evaluated. When three of

the five major components that define metabolic syndrome are present, the clinical evidence indicates that one or both forms of CV disease are present, at least in incipient form. To give maximum clinical benefit to the patient at risk, the clinician must be aware of these associations, look for them and institute the measures that can reduce the risk of progression.

Key Words: *Coronary artery disease; Insulin resistance; Lipoproteins; Metabolic syndrome; Obesity; Peripheral vascular disease*

Does true ‘metabolic syndrome’ (MS) exist, or is it just a collection of very frequent patient observations that may more appropriately be called a ‘clinical aggregate’ in a population with very poor health habits? Attempts to define such a concept began in 1988 when the term ‘syndrome X’ was coined to describe resistance to insulin-stimulated glucose uptake, hyperinsulinemia, hyperglycemia, increased very low-density lipoprotein (LDL), triglycerides, decreased high-density lipoprotein (HDL) and hypertension (1). Insulin resistance with compensatory hyperinsulinemia was subsequently suggested to be the causative factor.

Definition of MS

Further confusing the issue of whether the designation should be a syndrome or a clinical aggregate of observations is the fact that four different organizations have proposed varying criteria for ‘diagnosing’ MS (Table 1). To unify these criteria and provide guidance to the practising clinician, the syndrome/aggregate is defined as the presence of three of the five following entities (2): triglycerides greater than or equal to 150 mg/dL, HDL level lower than 40 mg/dL in men and lower than 50 mg/dL in women, blood pressure greater than or equal to 130/85 mmHg, waist girth greater than 102 cm (approximately 40 inches) in men or greater than 88 cm (approximately 34.5 inches) in women, and fasting glucose level greater than or equal to 100 mg/dL (also called ‘insulin resistance’). Other components with an association not quite so well established are the following: increased dense LDL, hyperuricemia, increased plasminogen activator inhibitor-1, increased high-sensitivity C-reactive protein, increased tissue necrosis factor-alpha, increased interleukin-6, resistin and decreased adiponectin. An important point is that each of the five major entities or components has been reported to have an association with increased levels of high-sensitivity C-reactive protein (3), which when present, appears to predict an increased risk of the two classifications of cardiovascular (CV) disease:

peripheral vascular disease (PVD) and coronary artery disease (CAD).

CV disease/MS association

There is a well-established overlap of PVD and CAD. In a study (4) of ankle-brachial index as a correlate of PVD in 273 patients with a mean age of 71 years, it was found that of 155 patients with a very low ankle-brachial index of less than 0.40, 130 (84%) had three- or four-vessel CAD. To show the interrelationship between MS and PVD, MS was noted in 59.8% of 388 patients with established PVD (5). Other measures to estimate the presence of PVD, such as carotid intima-media thickness, have also been shown to have an association with MS, with increased carotid intima-media thickness related to each MS component added (6). The correlation of MS directly with CAD and myocardial infarction (MI) has also been well established. Ninomiya et al (7) found the high association of MS with CAD confirmed by an OR of 2.01 for MI – markedly higher than with the individual components of MS. This association of MS with CAD holds up well even when using definitions of MS from various organizations (8). The OR for stroke in the presence of MS was even stronger at 2.16. Therefore, the association of MS/aggregate with both types of CV disease (CAD and PVD) is very high as supported by the clinical evidence cited. The physician caring for and the surgeon operating on CAD or PVD patients are obligated to be aware of the strong interrelationship of both CV diseases with MS and the need to aggressively treat/modify all components of MS present in each patient as part of essential preventive management.

Ford et al (9), using data from the National Cholesterol Education Program Adult Treatment Panel III, estimated that after age adjustment, 24% of adults in the United States have MS. Using the 2000 census as a standard reference population for age adjustment, this translates to 47 million residents. This group also noted a marked progression in incidence with age,

Division of Cardiovascular Medicine, Department of Medicine, Gill Heart Institute, University of Kentucky, Lexington, Kentucky, USA

Correspondence: Dr Thomas F Whayne Jr, Division of Cardiovascular Medicine, Department of Medicine, Gill Heart Institute, University of Kentucky, 326 Wethington Building, 900 South Limestone Street, Lexington, Kentucky 40536-0200, USA. Telephone 859-323-3705, fax 859-257-4845, e-mail tuhayn0@uky.edu

such that those older than 60 years of age exceeded an incidence rate of 40%. In addition, the National Cholesterol Education Program Adult Treatment Panel III (9) noted that the Mexican-American population appeared to have the highest total age-adjusted prevalence at 31.9%. This high prevalence of MS and the established presence in 59.8% of PVD patients (5) shows a clear connection between MS and PVD.

Is this highly prevalent group of components a true syndrome? Regardless of the answer and despite the lack of absolute confirmation that CV risk in the presence of these components is greater than the risk predicted by them as individual risk factors, emphasis on one of our nation's major medical problems using a term such as 'MS' is of significant value in risk management. Specifically, the term can be used to emphasize the risk of developing diabetes mellitus and CV disease when the syndrome's components are present, and the term can be used to promote prevention of abnormal levels of these components. On the other hand, designation as a syndrome also has major drawbacks. One is that some of the major risk factors for CV disease, such as tobacco abuse and LDL elevation, are entirely absent in the five criteria currently used for diagnosis of MS. Furthermore, certain vested interest groups, such as pharmaceutical companies, want to push the syndrome idea with associated treatment and specific medications for financial gain. All such considerations must be taken into account when assessing potential conflicts or commercial promotion versus clinical science.

MS and inflammatory markers

Chemokines can be defined as chemotactic cytokines that mediate inflammation (10). T lymphocytes (a type of leukocyte) locally release cytokines (11). Simplification of the definitions appears appropriate for the nonimmunologist trying to understand the relevance to CV disease. 'Cytokine' is derived from the Greek language meaning 'to set cells in motion', and cytokines/chemokines can be defined as intercellular signalling peptides released from stimulated leukocytes that act on other leukocyte targets (12). The T refers to the thymus as a primary source of these cells (13). T cells also play important roles in chronic inflammatory diseases, and multiple inflammatory cytokines/chemokines have been identified such as interleukin-6, C-reactive protein (the high-sensitivity form is relevant to atherosclerosis), serum amyloid P and tumour (also called tissue) necrosis factor- α (12). In atherosclerosis, macrophages and lymphocytes are the chief inflammatory cells found in diseased arteries (10).

The specific association of atherosclerosis has not been well studied in obesity. Wu et al (14) studied the effect of obesity on T cell expression, activation, secretion and upregulation in adipose tissue. Obesity is associated with chronic inflammation, which includes increased macrophage accumulation in adipose tissue associated with the upregulation of chemokines/cytokines. Wu et al (14) used flow cytometric analysis to show that an increased number of T cells and macrophages were present in the adipose tissue of diet-induced, obese, insulin-resistant male mice compared with lean mice and obese female mice ($P < 0.05$). Adiponectin-deficient mice were used. The sex difference in the obese mice was not satisfactorily explained because both were adiponectin deficient; a sex difference in the 21 human patients could not be assessed because only one patient was male. Flow

TABLE 1
Definition of the metabolic syndrome by four organizations after initial syndrome X definition

Organization	Definition
Syndrome X (1)	Insulin resistance, dyslipidemia, hypertension, obesity
WHO (28)	Insulin resistance plus two additional cardiovascular risk factors
European Group for the Study of Insulin Resistance (29)	Insulin resistance (plasma insulin in the upper quartile) plus two cardiovascular risk factors
International Diabetes Federation (30)	Abdominal obesity plus two additional National Cholesterol Education Program Adult Treatment Panel III risk factors
National Cholesterol Education Program Adult Treatment Panel III (2). This is the most prevalently used definition in the United States	Does not require insulin resistance or other individual factors; needs three of five specified factors: hypertriglyceridemia, low high-density lipoprotein, hypertension, obesity and increased glucose*

*Specific levels mentioned in the text

cytometric analysis indicated a male mice sex-dependent upregulation of messenger RNA (mRNA) and protein components of RANTES (regulated on activation, normal T cell expressed and secreted) and its receptor in the adipose tissue of obese male mice. In addition, the adipocytes of both male mice and humans expressed RANTES; the mRNA levels of RANTES were negatively correlated with the hormone adiponectin in the adipose tissues of these mice. Obese humans with MS had higher mRNA levels of RANTES and its receptor in subcutaneous adipose tissue than in lean humans. RANTES and the associated mRNA levels were significantly higher in visceral than subcutaneous adipose tissue of morbidly obese humans. It can be concluded that obesity is associated with increased accumulation of T cells and macrophages in adipose tissue, and this may play an important role in obesity-related disease by influencing preadipocyte/adipocyte functions. RANTES can be considered an adipokine that is upregulated in adipose tissue in both obese mice and obese humans (14). RANTES also fits in the classification of proinflammatory cytokine/chemokine (15). Such observations aid in the understanding of the interrelationship among MS, PVD and CAD.

MS and oxidative stress

There are experimental data to support the hypothesis that oxidized LDL is associated with MS, but data in humans have been lacking. Holvoet et al (16) assessed information from the Coronary Artery Risk Development in Young Adults (CARDIA) study. This was a population-based, prospective, observational study involving 1889 participants, 18 to 30 years of age, followed for 20 years. Incident MS was present in 12.9% of the subjects at the end of the 20-year interval; MS had not been present at the 15-year follow-up. Primary LDL concentration was not associated with this incident MS, whereas oxidized LDL was significantly associated. After adjustment for age, sex, ethnicity, tobacco abuse, body mass index, physical activity and primary LDL levels, the OR for MS in the five-year interval in the highest oxidized LDL quintile was 3.5 (95% CI 1.9 to 6.6), with a concentration greater than or equal to 97.4 U/L.

MS is a worldwide problem. In India, Sharma et al (17) studied oxidative stress specifically in MS patients. These patients had significantly lower levels of serum antioxidants measured by significantly low levels of the antioxidant vitamins A, C and E. This is of interest despite the failure to show deficiency of such vitamins to be a significant CV risk factor in some large studies (18). At the same time, there was a significant increase in oxidative stress with insulin resistance in MS. This oxidative stress was measured by thiobarbituric acid assay with results expressed as nmol of malondialdehyde formed. There appears to be sufficient evidence to suggest an association between MS and oxidative stress.

MS and mechanisms of CV disease

MS as a cause of CV disease has to be considered multifactorial. Each individual component, as discussed, has an association with CV disease. The precise progression depending on the number and type of component defining MS (2) has not been defined as a geometric or other type of progression. Nevertheless, the mechanisms are undoubtedly interrelated with each individual component, and their association with the various forms of CV disease is well established (4-8).

MS and asymptomatic CV disease

MS and its increased CV risk appears to have the same insidious association that is present with all forms of CV disease. The individual risk factors are, in general, silent and do not produce symptoms until the resultant CV disease has progressed significantly. This is well demonstrated by the American College of Cardiology/American Heart Association guidelines for the evaluation and management of chronic heart failure in the adult (19). In stage B, there is structural heart disease but no symptoms. The same applies to the atherosclerotic vulnerable plaque, which may be ready to rupture (20) but does not show any symptoms; in the case of CAD, a stress test would most likely be normal. These observations place even more emphasis on the necessity to favourably modify MS as a risk factor.

Risk reduction and management

The benefit from CV risk factor modification is well established. A major decrease in the LDL level to less than 70 mg/dL is the gold standard. There appears to be good data suggesting that even lower is better, as in the case of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) study (21). The groups with LDL levels lower than 40 mg/dL and with LDL levels between 40 mg/dL and 60 mg/dL had even fewer major cardiac events (death, MI, stroke, recurrent ischemia and revascularization) compared with higher LDL level groups. The West of Scotland Coronary Prevention Study Group (22) treated patients experiencing moderate hypercholesterolemia and no history of MI with pravastatin. The treatment significantly reduced the incidence of MI and death from CV causes in men with moderate hypercholesterolemia and no history of MI. There was no adverse effect on safety by the lower LDL levels achieved. Also, there was no adverse effect on the risk of death from non-CV causes. There are multiple other outcomes studies that support such risk factor management.

Risk factor management of MS components is essential and has also been shown to decrease CV events. Furthermore, risk reduction in women is just as important as it is in men (23). Therapy for MS is directed at the individual components. Such treatment includes therapeutic lifestyle modifications, blood lipid management and antihypertensive medications, especially those that alter the renin-angiotensin system. Results of various studies of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have demonstrated a decrease in new-onset diabetes and a reduction of CV events in a wide range of patients (24). Type 2 diabetes is a well-established, high-risk factor for CV disease, and its association with MS is also very strong (25). Approximately 13% of patients with diabetes do not have MS (ie, an association of approximately 87%). Therefore, global CV risk assessment is essential with adherence to current treatment guidelines for each of the risk factors (26). Nevertheless, there is still much to learn about the intensity of therapy such as that described in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (27). In this study, the use of intensive therapy to try to achieve normal glycated hemoglobin levels over 3.5 years did not significantly decrease major CV events and, in addition, an increase in total mortality was described. Diabetes control is warranted but outcome studies are always essential in CV disease, especially when intensive management is advocated. Nevertheless, overall risk factor management for CV disease is well supported with proof of extra benefit from aggressive management, as described in PROVE IT-TIMI 22 regarding intensive LDL lowering (21). Unfortunately, such outcomes from intensive management have not been shown with MS, but the data are nevertheless sufficient to support meticulous management.

CONCLUSIONS

Undoubtedly, the controversy over MS/aggregate of clinical observations in a population with poor health habits will continue while efforts are ongoing to elucidate and understand the true status. There is no doubt that there is a collection of abnormalities that appear to be both interrelated and linked to our population's health status, which on average is overweight, sedentary, includes a family history of high CV risk, and can be expected to have an increased incidence of hypertension, elevated blood glucose, decreased HDL, high triglycerides and obesity. What is important to understand is that 'MS' is a useful term, is not in itself a disease and that its management centres around individual treatment of each component that is present. This management is essential for CAD and PVD patients, whether under the direction of a surgeon, a cardiologist or an internist.

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