REVIEW

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Metabolic syndrome: Controversial but useful

ABSTRACT

The metabolic syndrome—the cluster of obesity, impaired fasting glucose, elevated triglycerides, low high-density lipoprotein cholesterol, and hypertension—may not be a "real" syndrome in the strict sense. It can, however, still be a useful concept if it prompts a physician to look for and treat additional risk factors when a patient is found to have one risk factor, or if it helps persuade patients to undertake healthy lifestyle changes before they develop overt diabetes mellitus or coronary artery disease.

KEY POINTS

Metabolic syndrome is very common and is associated with a risk of developing diabetes mellitus and cardiovascular disease. Not all studies, however, confirmed that the risk is greater than that predicted by individual risk factors.

At present, no unifying mechanism can explain the metabolic syndrome. Consequently, there is no unique treatment for it.

The two possible goals in treating metabolic syndrome are to prevent diabetes and to prevent cardiovascular disease. However, the definitions of metabolic syndrome ignore several strong risk factors for cardiovascular disease, such as cigarette smoking and elevated levels of low-density lipoprotein cholesterol.

The cornerstone of treatment should be lifestyle interventions: losing weight by eating less and exercising more.

METABOLIC SYNDROME is controversial. Critics point out that its definitions vary, it lacks a unifying mechanism, and there is little value in labeling this cluster of obesity, insulin resistance, dyslipidemia, and hypertension as a syndrome—we would do just as well to treat each risk factor individually.

Nevertheless, many people do have this combination of risk factors, and they are at substantially increased risk of developing diabetes mellitus and coronary artery disease.

This review examines the clinical utility of a defined metabolic syndrome in managing cardiovascular disease risk and discusses its physiologic basis.

DEFINITIONS VARY

In the latter half of the 20th century, risk factors for cardiovascular disease were identified and redefined to increasingly lower and tighter levels. Some of these risk factors, such as abdominal obesity, dyslipidemia, hypertension, and hyperglycemia, were observed to occur more frequently in patients with impaired glucose tolerance and type 2 diabetes. In 1988, Reaven named this cluster of metabolic risk factors "syndrome X."[1]

In 1998, the World Health Organization[2] and, later, the third Adult Treatment Panel of the National Cholesterol Education Program[3] and other organizations[4,5] developed consensus definitions of metabolic syndrome. Although these various definitions are similar in their values for triglycerides, high-density lipoprotein cholesterol (HDL-C), and blood pressure, they vary in how they define obesity and insulin resistance (**TABLE 1**). Furthermore, none of them addressed a potential unifying physiologic or

TABLE 1

Current definitions of metabolic syndrome differ

NCEP ATP III (≥ 3 CRITERIA)	AHA/NHLBI (3 CRITERIA)	IDF (OBESITY + ≥ 2 OTHER CRITERIA)	WHO (INSULIN RESISTANCE + ≥ 2 OTHER CRITERIA)
Waist circumference			**Body mass index**
> 40 in (102 cm) (men) > 35 in (88 cm) (women)	≥ 40 inches (men) ≥ 35 inches (women)	Ethnicity-specific*	> 30 kg/m^2 and/or **Waist-hip ratio** > 0.9 (men) > 0.85 (women)
Triglycerides			
≥ 150 mg/dL	≥ 150 mg/dL or treatment for hypertriglyceridemia	≥ 150 mg/dL or treatment for hypertriglyceridemia	≥ 150
High-density lipoprotein cholesterol (HDL-C)			
< 40 mg/dL (men) < 50 mg/dL (women)	< 40 mg/dL (men) < 50 mg/dL (women) or treatment for low HDL-C	< 40 mg/dL (men) < 50 mg/dL (women) or treatment for low HDL-C	< 35 mg/dL (men) < 40 mg/dL (women)
Blood pressure			
≥ 130/85 mm Hg or treatment for hypertension	≥ 135/85 mm Hg or treatment for hypertension	≥ 130/85 mm Hg or treatment for hypertension	≥ 140/90 mm Hg or treatment for hypertension
Fasting glucose			**Insulin resistance**
100–125 mg/dL	≥ 100 mg/dL or treatment for hyperglycemia	≥ 100 mg/dL or diagnosis of diabetes mellitus	Type 2 diabetes mellitus, impaired fasting glucose, impaired glucose tolerance
			Urinary albumin
			> 20 mg/mL
			Albumin-creatinine ratio
			> 30 mg/g

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III[3]
AHA/NHLBI = American Heart Association/National Heart, Lung, and Blood Institute[4]
IDF = International Diabetes Foundation[5]
WHO = World Health Organization[2]
*Europeans: men ≥ 94 cm, women ≥ 80 cm; South Asians: men ≥ 90 cm, women ≥ 80 cm; Chinese: men ≥ 90 cm, women ≥ 80 cm; Japanese: men ≥ 85 cm, women ≥ 90 cm; South and Central Americans: men ≥ 90 cm, women ≥ 80 cm; Sub-Saharan Africans: men ≥ 94 cm, women ≥ 80 cm; Eastern Mediterranean and Middle East (Arab) populations: men ≥ 94 cm, women ≥ 80 cm.

ADAPTED FROM VASUDEVAN AR, BALLANTYNE CM. CARDIOMETABOLIC RISK ASSESSMENT: AN APPROACH TO THE PREVENTION OF CARDIOVASCULAR DISEASE AND DIABETES MELLITUS.CLIN CORNERSTONE 2005; 7(2/3):7–16. WITH PERMISSION FROM EXCERPTA MEDICA, INC.

genetic mechanism for the syndrome, leading to confusion about how to detect and treat it.

IF METABOLIC SYNDROME IS REAL, WHAT CAUSES IT?

If metabolic syndrome is real, it should have a unifying physiologic mechanism, and its defining characteristics should have both mechanistic and clinical impact.

Insulin resistance?

At first, elevated levels of insulin were thought to be the mechanism driving the other components of the metabolic syndrome, and a potential target of therapy. Subsequently, attention

shifted to insulin resistance rather than insulin per se.[6]

However, only 78% of patients with metabolic syndrome have insulin resistance, and only 48% of people with insulin resistance have metabolic syndrome.[7]

Normally, the liver and muscles take up glucose in response to insulin. If this response is impaired, as in insulin resistance, the beta cells compensate by making more insulin, and blood glucose levels do not rise until the beta cells start to fail. Thus, although insulin resistance is mechanistically linked to the hyperglycemia seen in patients with metabolic syndrome, the beta-cell dysfunction is not a direct consequence of peripheral insulin resistance.

Furthermore, insulin resistance does not account for two other important mechanisms of cardiovascular disease: inflammation and hypercoagulability. Moreover, the dyslipidemia seen in patients with metabolic syndrome may actually be due to *enhanced* insulin action in the liver, leading to increased synthesis of very-low-density lipoprotein cholesterol (VLDL-C).

Abdominal obesity?

Obesity has always been assumed to be a major component of the metabolic syndrome, both as a criterion and perhaps as a causative mechanism. Reaven[8] points out that insulin resistance does not cause obesity; rather, obesity causes insulin resistance. However, insulin resistance also occurs in 10% to 15% of people who are not overweight.

But all fat is not the same. Intra-abdominal (visceral) fat has potential negative effects on metabolic and cardiovascular risk, while subcutaneous fat is metabolically and cardiovascularly inert and may actually serve a protective function. Dysfunction or insulin resistance of visceral fat is linked to the dyslipidemia, hypertension, hyperglycemia, and inflammation associated with metabolic syndrome.[4] Adipocyte dysfunction may be either intrinsic or secondary to immune dysregulation, inflammation, hypothalamic-pituitary-adrenal dysfunction, local glucocorticoid dysregulation within visceral fat, or, possibly, stress or energy imbalance. Adipocyte insulin resistance is no longer believed to be genetic but rather a consequence of hypertrophy of adipocytes, with resultant macrophage infiltration, inflammation, and alteration of adipocyte function.[9]

Abdominal obesity is harder to measure than one would think. Although there is a linear correlation between waist circumference and visceral fat, an increase of as little as 0.5 to 2 kg of visceral fat may be enough to induce adipocyte dysfunction but not enough to reach the Adult Treatment Panel or World Health Organization (WHO) criteria for obesity in the metabolic syndrome.[10] Furthermore, the distribution of visceral fat and therefore the criteria for abdominal obesity may be quite different in different ethnic groups.[11]

Free fatty acids?

A consequence of dysfunctional adipose tissue is that plasma levels of free fatty acids are chronically elevated. Free fatty acids are elevated normally during the fasting state, but insulin resistance in visceral fat cells leads to their chronic elevation in the postprandial state as well.[12]

In turn, chronic elevation of free fatty acids leads to decreased insulin sensitivity and reduced glucose uptake in other organs such as the liver and muscles, and to hyperglycemia by decreasing beta-cell function and accelerating apoptosis of pancreatic beta cells.[13]

If metabolic syndrome is real, it should have a unifying physiologic mechanism

Furthermore, increased flow of free fatty acids through the liver leads to accelerated synthesis of VLDL-C and hypertriglyceridemia. In patients with insulin resistance, triglyceride enrichment of HDL-C leads to accelerated HDL-C clearance and a decline in plasma HDL-C levels. Elevated free fatty acids have also been associated with endothelial dysfunction and vasoconstriction, leading to increases in blood pressure.[14]

However, increases in free fatty acids should be considered a characteristic of metabolic syndrome rather than a unifying mechanism. In fact, what we call insulin resistance in patients with metabolic syndrome is more truly a failure to suppress free fatty acids than a failure to take up glucose.

Inflammation?

Inflammation has been suggested as a cause of coronary artery disease. Increased levels of C-

reactive protein, a marker of inflammation, strongly predict coronary artery disease and are often present in patients with metabolic syndrome.[4] C-reactive protein levels increase with the number of metabolic risk factors in a given patient, and other inflammatory markers are increased as well in this syndrome. However, these associations are purely correlative, not causative, and the increased C-reactive protein seen in metabolic syndrome does not imply a mechanistic action.

METABOLIC SYNDROME IS COMMON

Metabolic syndrome poses a major public health concern, as it is common, and patients with this cluster of risk factors are at significantly increased risk of developing diabetes and cardiovascular disease.

Cardiovascular disease, the leading cause of death in the United States,[15] affects 70% or more of patients with type 2 diabetes, who have a four times higher incidence of cardiovascular events and death than do those without diabetes.[16] Even people with impaired glucose tolerance have a two times higher risk of cardiovascular disease and death.

In metabolic syndrome, the risk may not be greater than the sum of its parts

The prevalence of metabolic syndrome in healthy adults is between 15% and 23%,[17] but is much higher in Hispanics and African Americans, two groups with a markedly higher risk for diabetes and cardiovascular disease.

DOES METABOLIC SYNDROME PREDICT CARDIOVASCULAR DISEASE?

Evidence in favor

The Atherosclerosis Risk in Communities study found that the metabolic syndrome predicts future diabetes and cardiovascular disease, especially in women.[18]

In a study by Isomaa et al,[19] 12% of patients with metabolic syndrome died of coronary artery disease within 12 years, compared with 2.2% of controls.

The West of Scotland Coronary Prevention study[20] found that metabolic syndrome increased the risk of coronary heart disease by 76% and tripled the risk of diabetes.

The San Antonio Heart Study[21] found a risk of death due to coronary artery disease 2.5 times higher in people with metabolic syndrome in a healthy, predominantly Hispanic population.

The Copenhagen Male Study[22] found that hypertension markedly increased the risk of coronary artery disease in dyslipidemic patients but not in normolipidemic people, suggesting that the clustering of risk factors in metabolic syndrome does increase risk.

Evidence against

Not all epidemiologic studies found that the risk of coronary artery disease is higher in people with metabolic syndrome. Further, the individual components of the metabolic syndrome probably predict outcomes well enough, and the risk associated with the syndrome may not be greater than the sum of its parts.

Among Native Americans, a population at extremely high risk for type 2 diabetes, the Strong Heart Study failed to demonstrate an increased risk of coronary artery disease in people with metabolic syndrome beyond the risk predicted by individual risk factors.[23]

Bruno et al[24] found that 75.6% of a large series of patients with type 2 diabetes had metabolic syndrome, but metabolic syndrome did not predict cardiovascular death. Patients who had any one component of the syndrome had a risk of cardiovascular disease that was twice as high as in patients with none of the components. They concluded that categorizing the patients as having or not having the metabolic syndrome did not tell them anything beyond what they could predict from the individual components.

In assessing whether metabolic syndrome is a clinically useful tool, it is critical to look at it in patients with and without diabetes. When Wilson et al[25] removed hyperglycemia from the definition, they found that metabolic syndrome lost much of its predictive value for coronary artery disease.

In 18-year follow-up data from the Multiple Risk Factor Intervention Trial,[26] men with metabolic syndrome did have a higher risk than men without metabolic syndrome, but the risk rose incrementally with each additional risk factor, with no clinical reason for requiring three risk factors.

Metabolic syndrome omits important risk factors

The concept of a metabolic syndrome does not fit our current understanding of atherogenesis very well, omitting the two most potent predictors of cardiovascular disease risk—smoking and elevated low-density lipoprotein cholesterol (LDL-C) concentrations. Another risk factor, microalbuminuria, strongly predicts cardiovascular disease even in people without diabetes and is included in the WHO definition of metabolic syndrome, although it is not part of the more commonly used Adult Treatment Panel definition. Elevation of postprandial glucose above 140 mg/dL, which is not even part of the definition of metabolic syndrome, may ultimately predict cardiovascular and diabetes risk better than the other components.

Furthermore, the use of cut points to identify patients at risk is also arbitrary and implies a threshold of risk as opposed to a continuum of risk. Under the current definitions (TABLE 1), a 40-year-old man with an HDL-C level of 36 mg/dL, triglycerides 145 mg/dL, waist 37 inches, and fasting glucose 120 mg/dL would not be considered to have metabolic syndrome and therefore would not qualify for metabolic intervention. However, new guidelines may soon be forthcoming that will advocate aggressive management of his impaired fasting glucose and diabetes risk.

Therefore, treatment strategies will need to address unique risk factors in individual patients, rather than setting goals in an aggregate syndrome.

DOES METABOLIC SYNDROME PREDICT DIABETES?

Similarly, many have used metabolic syndrome to predict diabetes. Both Lorenzo et al in the San Antonio Heart Study[27] and Wilson et al in the Framingham offspring study[28] found that metabolic syndrome did predict future diabetes.

But other risk factors for diabetes are much stronger than metabolic syndrome.[29] Obesity, dyslipidemia, and hyperglycemia all correlate with insulin resistance, a necessary component of type 2 diabetes in 90% of cases. Impaired fasting glucose and impaired glucose tolerance are both associated with significant loss of beta-cell function.

With recent evidence from Ferrannini et al[30] showing that beta-cell loss actually begins while glucose tolerance is still normal, it is logical to assume that diabetes risk can be easily predicted from any combination of family history, hyperglycemia, and any marker of insulin resistance or inflammation, without the need to invoke the metabolic syndrome. Hemoglobin A_{1c} is an attractive option for screening, although it is less reliable at the low end of values, and no data for a threshold of risk yet exist.

TWO GOALS OF TREATMENT

In treating a patient who has metabolic syndrome, one has two possible objectives: to prevent diabetes and to prevent cardiovascular disease.

Since there is no unifying mechanism for the syndrome, there is no single pharmacologic intervention. For example, since not all patients are insulin-resistant, routine use of insulin sensitizers will not be cost-effective in many patients. However, obesity, insulin resistance, and fat cell dysfunction are all manifestations of caloric energy intake in excess of physical expenditure; hence, lifestyle interventions should have a profound impact.

Stress and depression may also be linked to metabolic syndrome mechanistically, but there is no evidence yet that intervention in these areas will reduce adverse clinical outcomes.[31]

Using cut points implies a threshold rather than a continuum of risk

To prevent diabetes

Lifestyle interventions clearly have the greatest impact of all the possible interventions, as shown in several studies. Most notably, in the Diabetes Prevention Program,[32] patients who managed to lose 7 kg and walk for 150 minutes per week reduced their risk of progressing to diabetes by 58%.

Metformin (Glucophage), which might seem to be an attractive option for preventing diabetes in metabolic syndrome, reduced risk by only 31% in the same study,[32] and had very modest effects on atherogenesis and no effects on dysfunctional fat cells, making its utility for patients with metabolic syndrome limited to those with polycystic ovarian syndrome or diabetes.

Thiazolidinediones may stabilize beta cells and, in several studies,[32,33] they reduced the incidence of progression to diabetes by 58% to 75%. These studies were of relatively short duration, and the cost-effectiveness of using these drugs to prevent diabetes in metabolic syndrome is unknown.

A strategy that could be used regardless of whether a patient has metabolic syndrome might be to monitor blood sugar levels more frequently in patients at risk and to use progressive interventions, starting with lifestyle changes and using beta-cell stabilizers if these fail.

To reduce cardiovascular risk

The issues involved in trying to prevent cardiovascular disease are similar to those in preventing diabetes. In young adults with a family history of premature cardiovascular disease and in patients with dyslipidemia, aggressive lifestyle modification and risk management should produce long-term benefit. However, since the absolute rates of cardiovascular events in patients with metabolic syndrome younger than 50 years are relatively low, it is difficult to demonstrate a benefit in the context of an individual practice. Each cardiovascular risk factor needs to be addressed individually rather than in aggregate.

Patients who lost 7 kg and walked for 150 minutes/week reduced their risk of diabetes by 58%

Lipid-lowering drugs. Only a few studies specifically looked at reducing the risk of cardiovascular disease in metabolic syndrome. Three studies, using statins, fibric acid derivatives, or a combination, all showed risk reduction, but not significantly greater than those predicted by lipid-lowering alone.[13] Therefore, when treating a patient with metabolic syndrome, the clinician should attempt to achieve four lipid targets:

- LDL-C lower than 100 mg/dL (the optimal level, per the Adult Treatment Panel guidelines[3])
- HDL-C higher than 35 mg/dL (HDL-C levels below 35 mg/dL increase the risk of cardiovascular disease fourfold, independent of other risk factors.[34])
- Triglycerides lower than 150 mg/dL (In the Paris study of impaired glucose tolerance and non-insulin-dependent diabetes, triglyceride levels above 125 mg/dL were associated with a twofold to fourfold increase in death rates.[35])
- Non-HDL-C lower than 130 mg/dL.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) have a role in treating metabolic syndrome in patients with hypertension, diabetes, or previous cardiovascular events. Several studies have demonstrated a reduction in both cardiovascular disease and progression to diabetes with these agents.[36] There is significant physiologic overlap in the mechanism by which ACE inhibitors, ARBs, thiazolidinediones, and statins reduce or prevent atherosclerosis, and it is unclear whether angiotensin-modifying drugs would have a major role in lower-risk patients with metabolic syndrome who do not have hypertension or cardiovascular disease.

Thiazolidinediones. Pioglitazone (Actos) reduced the incidence of cardiovascular disease in diabetic patients at high risk in the recent Prospective Pioglitazone Clinical Trials in Macrovascular Events (PROACTIVE) study.[37] The most pronounced reductions were in myocardial infarction and acute coronary syndrome.

If thiazolidinediones truly reduce cardiovascular risk, the mechanism may be by reducing glucose and lipid levels, blood pressure, adipocyte dysregulation, and inflammation. However, their utility in primary prevention is unknown, and their use in metabolic syndrome should be reserved for treating hyperglycemia if diet and exercise fail.

WHAT DOES METABOLIC SYNDROME MEAN TO THE CLINICIAN?

Metabolic syndrome has some use to the practicing clinician. Most cases of cardiovascular disease ultimately occur in patients with multiple risk factors, and most patients seen by a cardiologist are indeed insulin-resistant and have both adipocyte and macrophage dysfunction leading to inflammation. However, the current concept of metabolic syndrome may merely reflect the additive effects of three or more risk factors rather than a novel disease that requires unique screening.

If we could identify patient subgroups truly at risk of developing diabetes or cardiovascular disease, we might be able to intervene earlier and more cost-effectively, rather than screening and treating the general population.

As currently defined, metabolic syndrome is really more a late-stage marker of risk rather than an early-stage one.

Clearly, we need more specific markers of inflammation and adipocyte dysfunction than currently exist, especially in view of the variable definitions of metabolic syndrome. Although measuring hormones and cytokines such as adiponectin, plasminogen activator inhibitor I, and tumor necrosis factor alpha is attractive conceptually, they are still research tools, with no epidemiologic guidelines to help us integrate these measurements into clinical practice.

Until more outcome data are available, aggressive lifestyle intervention in patients at risk remains the most effective clinical strategy for the metabolic syndrome as currently defined. Dyslipidemia and worsening hyperglycemia should be treated aggressively with medications regardless of whether a "syndrome" is present.

The ultimate utility of even considering metabolic syndrome may simply be to provide patients and clinicians a framework in which to discuss the importance of multiple risk factors and interventions, especially if the patient has no symptoms and therefore is likely to be unmotivated and more likely to choose pharmacotherapy when ill than lifestyle changes before irreversible illness occurs.

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