

Metabolic Syndrome: What's in a name?

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Abstract

The term “metabolic syndrome” has recently become en vogue. But is the definition realistic, or helpful? This paper looks at the current definitions of metabolic syndrome and the bearing it has on clinicians both now and in the future.

Introduction

Over the past few years, clinicians have increasingly used the term “metabolic syndrome” to describe a patient at increased risk for cardiovascular disease (CVD) and type 2 diabetes. The metabolic syndrome consists of a constellation of risk factors, primarily abdominal obesity, hyperglycemia, low HDL, hypertriglyceridemia, and hypertension. These factors are associated with a number of other related risks such as high LDL, and prothrombotic and proinflammatory states.¹ Thus, the syndrome may be primarily used as an easier tool to identify individuals who need further testing for CVD risk factors and who need more intensive lifestyle counseling. The cause(s) of the syndrome remain obscure, but

insulin resistance may play a contributing role.¹⁻³

The naming of the metabolic syndrome has increased interest academically and clinically toward the roles of diet and physical activity in both the development and prevention of CVD. The strength of the metabolic syndrome appears in the ability to discuss the clustering of CVD risks with patients.⁴ However, as outlined in a recent review article by Kahn et al, the definition and use of the term metabolic syndrome also has many limitations.⁵ The purpose of this article is to discuss the varied definitions of the syndrome, the controversy surrounding its use, and its possible clinical utility.

Defining a Syndrome

Unfortunately, there is no clear consensus on the diagnostic criteria for metabolic syndrome, nor is there an agreement as to whether it actually exists as a separate entity apart from the sum of the component risk factors. However, because the syndrome helps to identify individuals at increased risk of type 2 diabetes and CVD, and because of the common treatment through lifestyle modifications, several large organizations have tried to formulate simple diagnostic criteria (Table 1).

The idea of a clustering of metabolic risk factors for diabetes and heart disease is over 80 years old,

but the World Health Organization (WHO) made the first attempted definition in 1998.⁶ This definition hinges on the importance of insulin resistance as well as 2 other criteria (Table 1). The European Group for the Study of Insulin Resistance modified the WHO definition to exclude overt diabetics and to require the presence of hyperinsulinemia. The Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III), published in 2001, is probably the most widely used definition clinically.¹ The focus of this definition is on CVD risk and requires 3 of 5 criteria. The International Diabetes Federation (IDF) made modifications to reflect a practical definition that can identify people worldwide at high risk for diabetes and CVD.⁷ This definition has incorporated ethnic-specific waist circumference cut-offs, as central obesity is deemed an essential component of the syndrome. Other variables included are similar to those in ATP III, with the newer impaired fasting glucose levels as defined by the American Diabetes Association.⁸

Although all definitions of the metabolic syndrome use similar criteria, important differences remain that cause confusion in the diagnosis and in the ability to compare populations and trends. In addition, there has been no identified review of the clinical evidence for either the criteria selected or the cut-off

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Table 1. Definitions of the Metabolic Syndrome

WHO ⁶	ATP III ¹	IDF ⁷
REQUIRED Diabetes, impaired fasting glucose, impaired glucose tolerance, OR insulin resistance (assessed by clamp studies)		REQUIRED Waist circumference, ethnicity specific
AND at least two of the following: Waist-to-hip ratio >0.90 in men and >0.85 in women	ANY three of the following: Waist circumference >102 cm in men and >88 cm in women	AND at least two of the following:
Serum triglycerides >150 mg/dL (1.7 mmol/l) OR HDL cholesterol <0.9 mmol/L in men and <1.0 mmol/L in women	Serum triglycerides >150 mg/dL (1.7 mmol/L)	Raised triglycerides >150 mg/dL (1.7 mmol/L) OR specific treatment for this lipid abnormality
Blood pressure >140/90 mmHg	Blood pressure >130/85 mmHg	Raised blood pressure: systolic >130 mmHG OR diastolic >85 mmHG OR treatment of previously diagnosed hypertension
Urinary albumin excretion rate >20 µg/min or albumin-to-creatinine ratio >30mg/g	HDL cholesterol <40 mg/dL (1.03 mmol/L) in men and <50 mg/dl (1.29 mmol/L) in women	Reduced HDL cholesterol <40 mg/dl (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women OR specific treatment for this lipid abnormality
	Serum glucose >110 mg/L (6.1 mmol/L) (>100 mg/dL or 5.6 mmol/L may be applicable)	Fasting plasma glucose >100 mg/dL (5.6 mmol/L) OR previously diagnosed Type 2 Diabetes

values.⁵ The definition of the metabolic syndrome is in flux precisely because the syndrome is itself in flux as more research becomes available about the etiology and connections between cardiovascular disease, diabetes, and obesity. Thus, these criteria are not the final word, but serve to aid in identification of people at increased risk.

Pathogenesis

The metabolic syndrome has been used as an important method to discuss potential common links of CVD risk factors, particularly the role of insulin resistance. However, research has found poor sensitivity,

specificity, and positive predictive value for predicting insulin resistance in nondiabetic individuals who have 3 or more metabolic syndrome traits.⁹⁻¹¹ New biochemical factors such as CRP and adiponectin, a marker from adipose tissue, are associated with insulin resistance,⁵ but are not part of the clinical criteria for the metabolic syndrome. Missing from the current definitions are also other strong clinical predictors of insulin resistance such as physical inactivity and aging.⁵ In addition, simpler models to identify patients with insulin resistance with better sensitivity and specificity exist, such as using body

mass index and family history of diabetes.¹² If researchers and clinicians are going to continue in the discussion of the etiology and best treatments for insulin resistance, then we need a clinical model that gives criteria at defined cut-off values that are metabolically linked.

Predicting Future Risk of Diabetes and CVD

Ample research has demonstrated the connection between the metabolic syndrome and the risk of both type 2 diabetes and CVD.⁵ However, many researchers argue that different algorithms could predict future risk better or as well as the metabolic syndrome.^{5,13} The presence of impaired fasting glucose is a simple measure and is just as effective at measuring risk of future diabetes.¹⁴ Predictors of CVD include algorithms such as the more complicated Framingham risk prediction model, and the use of strong yet simple clinical predictors alone such as age or fasting glucose.¹⁴ Patients with frank disease (i.e. diabetes, dyslipidemia, and hypertension) may still have an underlying common pathway of metabolic CVD risk factors. However, the current list of criteria does not calculate risk based on a gradient for various degrees of abnormalities, nor does the definition reflect possible differences in risk that occur with different combinations of criteria.⁵ The metabolic syndrome might be a more effective clinical risk predictor if there were differential predictive values for CVD based on a continuous scale, as seen with the Framingham model.⁵ Other potential drawbacks of using the metabolic syndrome as a predictor of future CVD include neglecting the contribution of other known risks such as age, family history, elevated LDL, low physical activity, and smoking; as well as labeling patients with another diagnosis.

Clinical Role in Diagnosis and Treatment

The metabolic syndrome may be clinically valuable to help providers recognize often overlooked CVD risk factors and to counsel patients regarding the effectiveness of lifestyle changes to reduce multiple risks simultaneously. The metabolic syndrome is also a way for clinicians to communicate the risk of overweight and obesity with patients who see excess weight as either the norm or as actually healthy. There is debate about whether the future risk of CVD is more than an addition of risks from the various metabolic syndrome criteria. Whether the risk is additive or multiplicative may not necessarily change the clinical usefulness of naming a syndrome that helps communicate to patients the preventive power of lifestyle changes.

Nevertheless, there has been no research investigating the effectiveness of using the metabolic syndrome as a tool to diagnose patients with high CVD risk and/or the need for lifestyle counseling. Does the label help motivate practitioners and patients to engage in lifestyle counseling? Does adding the label to patients who already have a known disease, such as diabetes or hypertension, help focus on the need for lifestyle changes even after medication therapy has started? In addition, the question remains as to whether clinicians would then be more likely to use lifestyle counseling only for patients with the metabolic syndrome and neglect those with fewer or other CVD risks. In our opinion, identifying patients with the metabolic syndrome is not the only method for choosing which patients need lifestyle counseling, but rather is an additional method for identifying patients who might otherwise be missed due to multiple borderline values. Perhaps the clinical use of

the metabolic syndrome could be restricted to patients who only have borderline values, and do not meet the criteria yet for any disease.¹⁵

There is no debate about the importance of aggressive lifestyle modification. However, healthy diets and physical activity are necessary for patients with only 1 CVD risk too, not just those with the metabolic syndrome. Multiple trials show that lifestyle modification reduces the risk for future diabetes in patients with impaired fasting glucose (100-125 mg/dL) and impaired glucose tolerance (140-199 mg/dL 2 hours after a 75-gram oral glucose load) alone.¹⁶ Current guidelines for elevated blood pressure and dyslipidemias also include recommendations for lifestyle counseling as a basic tenet of therapy.^{1,17} The United States Preventive Services Task Force (USPSTF) found at least fair evidence, and more benefit than harm, in providing intensive lifestyle counseling and behavioral interventions to people with obesity.¹⁸ However, the USPSTF recognizes the current limitations in primary care practices to provide intensive lifestyle counseling.¹⁹

Future Research Needed

A greater understanding of what risks are linked to insulin resistance and/or visceral adiposity, and what risks are the most predictive of CVD and the most amenable to treatment and/or prevention, are important research areas. We also need basic office-based research on whether or not the use of another diagnostic label is helpful for clinicians or patients in discussion of CVD risk and the need for lifestyle changes. Factors such as inflammatory markers (C-reactive protein, tumor necrosis factor alpha, interleukin 6), LDL, biomarkers of adipose tissue (adiponectin, leptin), and thrombotic markers (fibrinogen, plasminogen activator

inhibitor type 1) will be important targets for further investigation.^{3,7} Future research will lead to more accurate predictive indices of both insulin resistance and overall CVD risk, and will thereby guide more specific treatment recommendations. If there is truly an underlying etiology such as insulin resistance, then medications that treat insulin resistance may be added to patients with the metabolic syndrome if lifestyle modifications fail. In patients who only had insulin resistance and no more than 1 other criteria at baseline, the Diabetes Prevention Program found that lifestyle modification, as well as metformin to a lesser extent, reduced the development of the metabolic syndrome.²⁰

Conclusion

Overall, we feel that the metabolic syndrome can be a useful clinical concept to assist clinicians and patients in understanding the importance of lifestyle change in reducing risk for diabetes and CVD. However, the syndrome should not be used as the only determination of patients at high-risk of diabetes and CVD. In fact, other clinical risk predictors may be better at estimating risk of future disease. In addition, the syndrome should not be used as the only determination of who needs lifestyle counseling. Most patients with any CVD risk need help achieving essential lifestyle modifications. Further research is needed to determine the utility of the metabolic syndrome both as a clinical and research construct. And beware that the definition will likely change as more research is done.

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