Review Article

The Relevance of the Metabolic Syndrome

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Abstract

Introduction: To review the definitions of the metabolic syndrome according to various expert groups and assess their relevance to clinical practice. Materials and Methods: Medline searches were conducted to identify studies which addressed: (i) the utility of the metabolic syndrome compared to multivariable predictive functions for the identification of individuals at high risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), (ii) the importance and definition of obesity in the definition of the metabolic syndrome and (iii) the impact of lifestyle and pharmacological interventions designed to reduce the risk of cardiovascular disease in those with and without the metabolic syndrome. Results: Although inferior to multivariable risk scores in predicting T2DM and CVD, the metabolic syndrome represents a simple clinical tool, particularly for the prediction of T2DM. Obesity is not a critical component of the metabolic syndrome for identifying those at increased risk of CVD but may be important for predicting T2DM. If anything, pharmacological therapy, especially lipid lowering is as, if not more, effective in those with the metabolic syndrome than in those without. Conclusions: Although the metabolic syndrome appears to have limited utility for the identification of individuals at increased risk of T2DM or CVD, the diagnosis of the metabolic syndrome presents an opportunity to rationalise health services to deliver coordinated care to those with metabolic syndrome.

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Introduction

Metabolic syndrome describes a constellation of interrelated metabolic risk factors, in which components coexist more frequently in a given individual than could be expected by chance alone. These risk factors include hypertension, hyperglycaemia, dyslipidaemia and obesity. The underlying pathophysiology is as yet unclear, but has been closely linked to insulin resistance and obesity.[1-5] Several expert groups have attempted to define the metabolic syndrome with the aim of establishing working diagnostic criteria that is applicable in clinical practice. The various criteria are found in Table 1.

As we can see, many different diagnostic criteria have been used. However, the simplest to implement in a clinical setting are those from the American Heart Association and the National Heart, Lung and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF). They have also been most frequently applied in a large number of studies.

The AHA/NHLBI recommendation for the diagnosis of the metabolic syndrome was based on a definition that was initially suggested by the National Cholesterol Education Program-Adult Treatment Panel (NCEP ATP III). In making these recommendations, the ATP III had a goal of identifying people at higher long-term risk for atherosclerotic cardiovascular disease (CVD) and who deserved clinical lifestyle intervention to reduce risk.[3] The IDF states that the ultimate importance of metabolic syndrome is that it helps identify individuals at high risk of both type 2 diabetes mellitus (T2DM) and CVD.[4,5]

In this review, we will attempt to determine if the definitions of the metabolic syndrome, as they stand today, achieve these goals, and how such a definition might be useful in present clinical practice.

Metabolic Syndrome as a Predictor of Cardiovascular Disease and Diabetes Mellitus

The metabolic syndrome has been shown to be associated

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Table 1. Criteria for Diagnosis of the Metabolic Syndrome

Clinical measure	WHO (1998)	EGIR	NCEP ATP III (2001)	AACE (2003)	IDF (2005)	AHA/NHLBI (2005)
Insulin resistance	IGT, IFG, T2DM or lowered insulin sensitivity* Plus any 2 of the following	Plasma insulin >75th percentile Plus any 2 of the following	None. But any 3 of following 5 features	IGT or IFG Plus any of the following based on clinical judgment.	None	None. But any 3 of following 5 features
Obesity	WHR: Men ≥0.9 Women ≥0.85 And/or BMI >30 kg/m^2	WC: Men ≥94cm Women ≥80cm	WC: Men ≥102cm† Women ≥88cm	BMI ≥25kg/m^2	Increased WC (population specific). Plus any 2 of the following	WC: Men ≥102 cm Women ≥88 cm
Dyslipidaemia	TG ≥150 mg/dL and/or HDL-C: Men ≤35 mg/dL Women ≤39 mg/dL	TG ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TG ≥150 mg/dL HDL-C: Men ≤40 mg/dL Women ≤50 mg/dL	TG ≥150mg/dL and HDL-C: Men <40 mg/dL Women <50 mg/dL	TG ≥150 mg/dL or on TG Rx HDL-C: Men ≤40 mg/dL Women ≤50 mg/dL or on HDL-C Rx	TG ≥150 mg/dL or on TG Rx HDL-C: Men ≤40 mg/dL Women ≤50 mg/dL or on HDL-C Rx
Blood pressure	≥140/90 mmHg	≥140/90 mmHg or on hypertension Rx	≥130/85 mmHg	≥130/85 mmHg	SBP ≥130 mmHg or DBP ≥85 mmHg or on hypertension Rx	SBP ≥130 mmHg or DBP ≥85 mmHg or on hypertension Rx
Glucose	IGT, IFG or T2DM	IGT or IFG (but not diabetes)	>110 mg/dL‡ includes diabetes	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes)	≥100 mg/dL or on Rx for elevated glucose
Other	Microalbuminuria			Other features of insulin resistance§		

AACE: American Association of Clinical Endocrinology
AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute
BMI: body mass index
DBP: diastolic blood pressure
EGIR: European Group for the Study of Insulin Resistance
HDL-C: high density lipoprotein cholesterol
IDF: International Diabetes Federation
IFG: impaired fasting glucose
IGT: impaired glucose tolerance
NCEP ATP III: National Cholesterol Education Program-Adult Treatment Panel
SBP: systolic blood pressure
TG: triglycerides
T2DM: type 2 diabetes mellitus
WHO: World Health Organization
WC: waist circumference
WHR: waist-hip-ratio

* Insulin sensitivity measure under hyperinsulinaemic euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation

† Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased e.g. 94 to 102 cm. Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference.

‡ The 2001 definition identified fasting glucose of ≥110 mg/dL (6.1 mmol/L) as elevated. This was modified in 2004 to be ≥100 mg/dL (5.6 mmol/L), in accordance with the American Diabetes Association's updated definition of IFG.

§ Includes family history of type 2 diabetes mellitus, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to type 2 diabetes mellitus.

with both increased risk of T2DM and CVD in multiple studies using a variety of definitions.[7] This is also true in the population of Singapore, where our studies have shown that the metabolic syndrome is associated with an increased risk of CVD,[8] as well as all-cause mortality and mortality from CVD.[9] This should not come as a surprise, given that each of the components of the metabolic syndrome is an independent risk factor for these diseases. It stands to reason that the presence of multiple risk factors would connote a higher risk of disease.

What is not clear is whether the metabolic syndrome is the most effective way of identifying individuals at risk of CVD or DM. A number of studies have evaluated this.

Stern et al,[10] using a population-based sample of initially non-diabetic San Antonio Heart Study participants and a

similar sample from the Mexico City Diabetes Study, showed that the metabolic syndrome was inferior to the Framingham risk score in its ability to discriminate between those at high and low risk of developing future CVD. They also found that the metabolic syndrome was less effective at discriminating between those at high or low risk of developing T2DM compared to a predictive model developed from the San Antonio Heart Study.

This was further confirmed in a study by Wannamethee et al which compared the metabolic syndrome with the Framingham risk score as predictors of coronary heart disease, stroke and T2DM. They found that the Framingham risk score was a better predictor of coronary heart disease and stroke than the metabolic syndrome but was less predictive of T2DM.[11] It should be noted however, that the Framingham risk score was not developed to predict T2DM. Whereas in the study by Stern et al, the comparison was between the metabolic syndrome and a specific predictive function for identifying persons at an increased risk of T2DM.

Finally, McNeill et al found that including the metabolic syndrome as an additional variable in a predictive function provided little advantage over and above the Framingham risk function alone.[12]

As a predictor of CVD or T2DM, the metabolic syndrome seems to provide little advantage over risk functions that have been developed specifically for these conditions. There are several possible reasons for this including the fact that many important and established risk factors are not included in the definitions of the metabolic syndrome. For CVD, these include age, smoking and (low density lipoprotein- cholesterol) LDL-cholesterol, all of which are important predictors of the future risk of CVD events. For T2DM, most predictive functions would include a family history of T2DM as a contributing factor.

Furthermore, most of the risk factors included in the metabolic syndrome show a linear and continuous association with an increased risk of CVD or T2DM. In the definition of the metabolic syndrome, these are all treated as dichotomous variables which may limit the precision with which it predicts the future risk of CVD or T2DM.

On the other hand, as practicing physicians, we are familiar with dichotomising risk factors. Hypertension, T2DM, being overweight and obesity are all definitions used commonly in clinical practice and each represents an instance where a continuous risk factor has been dichotomised. As such, until the risk scores such as the Framingham risk score become routinely used in clinical practice, the metabolic syndrome may represent a simple convenient way, in which individuals at increased risk of CVD or T2DM can be identified.

In addition, one has to consider that while the Framingham risk score has been extensively validated and showed to be applicable to a number of populations,[13-15] this is not the case for predictive functions for T2DM, which have only begun to be explored in a number of populations.[16-18] As such, the metabolic syndrome may have a special place, at this time, for identifying individuals at high risk of developing T2DM.

Having said that, if it is to be used as a predictor of T2DM, then the definition must exclude those with established T2DM, which is currently not the case with either the AHA/NHLBI or IDF criteria for the diagnosis of the metabolic syndrome.

Obesity as a Feature of the Metabolic Syndrome

Over and above the issues related to the ability of the metabolic syndrome to predict CVD and T2DM, the definition of obesity and the manner of its inclusion as a diagnostic criterion has generated some controversy. In both the AHA/NHLBI and the IDF recommendations, different cut-offs for waist circumference have been recommended for various ethnic groups.

This approach has been criticised on the basis that "it is not known if the same amount of intra-abdominal fat mass carries different risk in different ethnic groups".[19] It is likely that this criticism represents a failure to understand the basis upon which these ethnic specific recommendations have been made. These recommendations in fact, do not represent a belief that the same amount of intra-abdominal fat mass carries different risks in different ethnic groups. Rather, it represents the observation that the relationship between anthropometric measures of obesity (body mass index or waist circumference) and adiposity, differs between ethnic groups. For example, persons in Singapore have a greater degree of adiposity than Caucasians, for the same body mass index.[20] More recently, this ethic difference has been applied to waist circumference and it has been shown that for the same waist circumference, individuals of different ethnic backgrounds carry different amounts of intra-abdominal fat.[21-23] As such, the use of the same waist circumference cut-off in different ethnic groups may result in a systematic over- or under-estimation of intra-abdominal fat mass. We believe that the application of ethnic specific cut-offs, as recommended, may identify individuals with similar amounts of intra-abdominal fat across various ethnic groups.

In line with this finding, we have shown that the use of these ethnic specific cut-offs in Asians is associated with an odds ratio of 2.87 for ischaemic heart disease,[8] a magnitude that is similar, or greater, than the risk of CVD associated with the metabolic syndrome in Caucasian populations.

Another issue pertains to the IDF recommendation that

obesity is required to be present, in addition to 2 other features, for the diagnosis of metabolic syndrome. In contrast, the AHA/NHLBI allows the diagnosis of the metabolic syndrome in the presence of any 3 criteria, which may or may not include obesity. We have shown that, in the Singapore population, approximately 10% to 13% of men and 2% to 4% of women, exhibit 3 or more features of the metabolic syndrome in the absence of central obesity.[24] In addition, we have also shown that these individuals, show similar levels of risk for CVD, whether or not obesity is present as a feature of the metabolic syndrome.[25] Having said that, our studies also showed that the presence of obesity as a pre-requisite for diagnosing the metabolic syndrome may identify individuals with greater degrees of insulin resistance and hyperglycemia.[24] This suggests that the IDF definition may be more suited to identifying individuals at risk of future T2DM. However, this has yet to be substantiated in prospective studies.

Reducing the Risk of CVD in Those with Metabolic Syndrome

The ATPIII has suggested that identification of individuals with the metabolic syndrome will allow recognition of those who deserved clinical lifestyle intervention in order to reduce risk.[3] In order to assess the utility of the metabolic syndrome in this context, we asked the following questions: (i) Is there any evidence that lifestyle intervention is particularly efficacious in reducing CVD risk in those with the metabolic syndrome, and (ii) Are pharmacological therapies that reduce CVD risk less effective in those with the metabolic syndrome? These questions are relevant since lifestyle intervention is recommended as the first step in reducing the impact of most cardiovascular risk factors including all those that form part of the metabolic syndrome.

There have been no studies that have examined the impact of lifestyle modification on the risk of CVD events or incident T2DM in those with and without the metabolic syndrome. One study (The PREMIER Clinical Trial) examined the effects of intensive behavioural intervention with or without the Dietary Approaches to Stop Hypertension (DASH) diet, in patients with mild hypertension, with and without the metabolic syndrome.[26] The results of that study suggested that intensive behavioural intervention, used alone, was less effective in lowering blood pressure in those with the metabolic syndrome than in those without. If anything, this suggests that any lifestyle intervention in those with the metabolic syndrome may need to be more intensive than in those without.

In relation to the second question, post-hoc analyses of several lipid-lowering trials have compared the efficacy of treatment in those with and without the metabolic syndrome. Several of the statin trials have shown that the efficacy of statin therapy results in a similar, if not greater, relative risk reduction for CVD events in those with the metabolic syndrome, compared to that without.[27-31] However, these studies also showed a higher absolute risk of CVD in those with the metabolic syndrome. As a consequence, the absolute risk reduction is greater (and the number needed to treat smaller) in those with the metabolic syndrome compared to those without. Similar findings were noted with nicotinic acid in the coronary drug project.[32]

The situation is different with fibrate therapy. The Bezafibrate Infarction Prevention Study found that treatment with bezafibrate in individuals with established coronary artery disease did not reduce all-cause or cardiac mortality in the entire population,[33] but in those with the metabolic syndrome, treatment was associated with a reduction in cardiac mortality risk with a hazard ratio of 0.74. In the same study, analysis of patients with 4 or 5 metabolic risk factors showed an even more marked risk reduction.[34]

Conclusion

The metabolic syndrome does identify individuals at increased risk of CVD and T2DM in our population as in most populations studied. The simplicity of the definitions makes it attractive for use in clinical practice. However, it should be borne in mind that as a predictor of both CVD and T2DM, it performs less well than multi-variable predictive functions specifically derived for the identification of persons at high risk of these conditions. Existing data does not appear to suggest that lifestyle modification is particularly efficacious in those with the metabolic syndrome. If anything, drug treatment (particularly in relation to the treatment of dyslipidemia) may be particularly effective in this group of individuals. One seldom considered utility of the metabolic syndrome is that its diagnosis presents an opportunity to rationalise health services to deliver coordinated care to those with the metabolic syndrome instead of sub-dividing the care into separate services addressing hyperglycaemia, obesity, blood pressure and dyslipidaemia, individually.[35] We are, after all, treating patients and not cardiovascular risk factors.

Alternatively, if indeed there is a single pathophysiologic mechanism underlying this cluster of metabolic derangements, the identification of this "common soil" may present opportunities for the development of therapeutic options with efficacy in treating multiple traits simultaneously.

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