Metabolic syndrome

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Introduction

Metabolic syndrome (MetS) is a common disorder characterized by the clustering of risk factors for developing cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Though the idea of MetS has existed for over 80 years, the concept was not further developed until 1988; since then our understanding of this disorder has been continuously evolving. The precise definition and criteria for diagnosis of MetS has been rapidly changing in recent years.¹⁻³

The signs that characterize MetS include central obesity, dyslipidemia, hyperglycemia and hypertension. It is believed that the diagnosis of MetS is a greater predictor for the development of CVD and T2DM than the consideration of these risk factors independently.⁴ In keeping with its classification as a ‘syndrome,’ there has not been a single cause identified in the etiology of MetS, and there is still much that is unknown about its pathophysiology. Indeed, it is even unclear whether MetS is a ‘true’ syndrome where the symptoms are related by pathophysiology, or whether the disorder is simply a collection of common independent risk factors from differing disease phenotypes.⁵ Nevertheless, insulin resistance is the most commonly accepted mechanism through which MetS develops.⁶

There have been many definitions of MetS released by separate institutions since the WHO released the first formalized criteria in 1999. Each of the criteria considers similar parameters that reflect both our understanding in the pathophysiology of MetS, as well as the clinical presentation of the disorder. There are differences between guidelines in cutoff values and the combinations of symptoms that will allow a diagnosis. This article will review three guidelines – the WHO, ATP III and the IDF – as these appear to be the most commonly used criteria in the current literature.

Current guidelines – review and comparison

The specific details of the criteria are summarized in Table 1 for comparison. The first set of diagnostic criteria was put forth by the WHO diabetes group in 1999. Insulin resistance or impaired glucose tolerance or diabetes, hypertension, dyslipidemia, obesity and microalbuminuria were defined as the components of MetS.¹ These criteria were felt to be difficult to measure in the clinic; the oral glucose tolerance test and albumin measurement were not feasible tests that could be easily done in the clinic. In response, the US National Cholesterol Education Program: Adult Treatment Panel III (NCEP:ATP III or ATP III) in 2001 released a new set of criteria where insulin resistance was measured by a fasting glucose test, a simpler test than the oral glucose tolerance test. The combination of risk factors and cut-off levels also differed from the WHO criteria. The ATP III criteria, however, still had their shortcomings. Although easier to use in the clinic, the ATP III guidelines were not suitable for an international population; for example, ethnic differences in BMI were not addressed.

In 2004, in order to clear the confusion between multiple guidelines and to create an internationally applicable guideline, the International Diabetes Federation released a unified definition in 2005 (updated in 2006).³ Like the ATP III, the IDF used criteria that could be easily tested in the clinic. The most significant change in the IDF criteria was the use of central obesity as a necessary component for diagnosis. Also important was the attempt to make the criteria applicable for a worldwide population by releasing cut-off levels for central obesity that were specific for different ethnicities. The cutoff values were generally lower than levels present in the other criteria, and the specific values were obtained using anthropometric studies of different populations.⁷

In addition to the three guidelines that have been outlined, it is important to note other guidelines released by institutions such as the American Association of Endocrinology, the National Heart, Lung, and Blood Institute (NHLBI). These are all similar, but differ slightly in cutoff levels.

Prevalence and predictive value

MetS is a very common disorder. The literature suggests a prevalence ranging from 14-32%.⁶⁻⁷ Specific prevalence depends on geographic location, population characteristics such as ethnicity, and the criteria used to define MetS. The majority of studies suggest that a higher prevalence of MetS is identified using the IDF criteria than the ATP III criteria.⁶⁻⁷

The importance of MetS lies in its ability to predict more significant disease, primarily T2DM and CVD. While there is strong evidence to suggest that MetS is a good predictor of T2DM, the ability to predict CVD in MetS is controversial.⁸ In addition to T2DM and CVD there have also been studies suggesting that MetS can predict other diseases and outcomes, including chronic kidney disease, sexual dysfunction, hypogonadism, polycystic ovarian syndrome (PCOS), fatty liver and all-cause mortality.⁹⁻¹¹

The literature suggests that MetS is a strong predictor of developing T2DM. The specific predictive ability differs between different studies and between criteria. A number of separate studies have compared the ability of the ATP III criteria and the IDF criteria in predicting diabetes in different populations. In the articles reviewed, the predictive value of MetS ranges, with articles listing an increased RR of 3.08 all the way to 10.10.⁷⁻¹¹ Comparing sets of
Diagnostic review

Metabolic syndrome criteria, it has been suggested that the ATPIII criteria appears to be more effective at predicting diabetes but these results are not necessarily definitive. In comparison to established methods for predicting diabetes, studies have found no advantage. MetS using the ATPIII criteria shows a lower sensitivity and a higher false-positive rate when compared to the Diabetes Risk Score, a standard method to measure risk of developing diabetes.

Whether MetS is able to predict CVD is unclear and controversial. The MetS criteria does not include absolute CVD risk factors that are included in standardized risk assessment methods such as age, smoking, and family history. Regardless, studies have shown that individuals diagnosed with MetS do show a statistical increase in developing CVD, and that it is an important risk factor for CVD cause and mortality. When compared to existing methods for predicting CVD, one study demonstrated that a diagnosis of MetS had a lower sensitivity and higher false-positive rate compared to the Framingham Score in predicting CVD.

Other studies suggest that despite the ability of MetS to predict CVD mortality, it does not do so beyond the ability of its individual components.

Discussion

MetS identifies individuals that are at risk of developing CVD and T2DM, but its ability to do so is confounded by the existence of multiple criteria, and a lack of knowledge of this disorder. A formal definition of MetS was created only in the last 10 years, and there have been few long-term studies on MetS. The resulting lack of evidence and an incomplete knowledge of its pathophysiology are also significant sources of confusion. While MetS is able to predict diabetes and CVD to an extent, its efficiency and effectiveness are controversial. For instance, the IDF criteria has been criticized for missing high risk patients that do not show central obesity. The ability of MetS to predict disease has been shown to be no more effective than existing methods. Other studies suggest that the risk associated with MetS is no greater than the risk associated with its individual components. This brings into question the clinical value of diagnosing MetS.

Nevertheless, there is convincing evidence for the use of MetS. Recently, a report has been published supporting the use of MetS as an important public health tool. It acknowledges the limitations that MetS has in predicting DM and CVD, but it also stresses that combined with other clinical tools and other existing guidelines, MetS can be useful in helping patients understand their level of risk and its potential impact on their health in the future. Underlining how separate risk factors can be interrelated can have an important role in helping both clinicians and patients address risk factors, especially if lifestyle modification is the goal.

Recent research has been focused on addressing the limitations and confusion that surrounds MetS. Most recently, in October, the IDF and AHA have jointly released a new guideline that attempts to unify the MetS criteria. Other areas of recent research include establishing more evidence to better refine the MetS criteria, with a particular focus in different subpopulation and ethnic groups. With the incidence of childhood T2DM on the rise, there is a need to develop standardized criteria for MetS diagnosis in the pediatric population.

In summary, MetS is a useful tool to identify individuals at risk for developing T2DM and CV. There are many

<table>
<thead>
<tr>
<th>WHO</th>
<th>ATP III</th>
<th>IDF</th>
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<tbody>
<tr>
<td>Impaired glucose tolerance or insulin resistance or a diagnosis of T2DM</td>
<td>Any three or more of the following:</td>
<td>Central obesity w/ ethnic specific values or BMI&gt; 30</td>
</tr>
<tr>
<td>Plus any two of the following:</td>
<td>Raised Triglycerides ≥ 1.7 mmol/L</td>
<td>Raised Triglycerides ≥ 1.7 mmol/L</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Reduced HDL cholesterol</td>
<td>Reduced HDL cholesterol</td>
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<tr>
<td>Triglycerides ≥ 1.7 mmol/L</td>
<td>&lt; 1.03 mmol/L (males)</td>
<td>&lt; 1.03 mmol/L (males)</td>
</tr>
<tr>
<td>or HDL&lt;0.9 mmol/L (males)</td>
<td>&lt; 1.29 mmol/L (females)</td>
<td>&lt; 1.29 mmol/L (females)</td>
</tr>
<tr>
<td>or HDL&lt;1.0 mmol/L (females)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Hypertension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Albumin excretion &gt; 20µg/min</td>
<td>≥130 systolic or ≥85 diastolic (mmHg)</td>
<td>≥130 systolic or ≥85 diastolic (mmHg)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Raised fasting plasma glucose</td>
<td>Raised fasting plasma glucose</td>
</tr>
<tr>
<td>&gt;140/90 mmHg</td>
<td></td>
<td>Fasting plasma glucose ≥100mg/dL</td>
</tr>
<tr>
<td>Obesity</td>
<td>Central Obesity</td>
<td>or previously diagnosed T2DM</td>
</tr>
<tr>
<td>BMI &gt; 30 or waist:hip ratio &gt; 0.9 in males, &gt;0.85 in females</td>
<td>&gt;102 cm (male), &gt;88cm (female)</td>
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Table 1. Summary of the WHO, ATPIII and IDF criteria for metabolic syndrome
issues that limit its clinical value, including confusion between the existence of multiple guidelines, controversy in the research, lack of evidence, and a poor understanding of its pathophysiology. Nevertheless, it is important to appreciate the function of MetS, especially as the incidence of CVD and T2DM continues to rise in today’s society.

References


7. Yoon YS, Lee ES, Park C, et al. The new definition of metabolic syndrome by the international diabetes federation is less likely to identify metabolically abnormal but non-obese individuals than the definition by the revised national cholesterol education program: the Korea NHANES study. Int J Obes (Lond) 2007 March;31(3):528-34.


