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Review

Here we go again ... The metabolic syndrome revisited!

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ABSTRACT

Whilst all innovations and new ideas will have their passionate proponents, one of the *sine qua non* of the medical world is that it will also have its opponents. The concept of the metabolic syndrome was no exception and went through its debates and controversies. With the harmonization between the AHA/NHLBI and the IDF definitions for the diagnosis of the metabolic syndrome, one would have hoped that that we would now take a step forward and thrash out a consensus on the metabolic syndrome between the opponents and the proponents so that we could leave this controversy behind us. But a WHO Expert Consultation Group recently came out with a report which basically reiterated the old arguments, though in a more nuanced manner, which had been used by those opposing the concept of the metabolic syndrome from its initial stages. The report points out that, despite an exponential increase in the number of research papers on the subject, no single unifying pathophysiological mechanism has been agreed, and the equivalence of the risk factors and their cutoff points across different populations has not been established. The criteria used to diagnose the metabolic syndrome have major limitations including: the dichotomisation of risk factors; the attribution of relative as opposed to absolute risk; the differing predictive value of risk factor combinations; the inclusion of individuals with established diabetes and heart disease; and the omission of important risk factors for predicting diabetes and CVD. A formal diagnosis of the metabolic syndrome is rarely made in routine clinical practice, and the concept has not been widely adopted in national guidelines for the prediction of CVD or diabetes. The end recommendation was that whilst, it may be considered useful as an educational concept, it should be considered a premorbid condition with limited practical utility as a diagnostic or management tool. Many of these questions have been answered in the past. The need of the hour is not too guard one's turf or come out with controversial statements, which frankly are no more than hindrances at least in this instance, but accept that we are facing a major problem as far as the ravages associated with T2DM and ASCVD are concerned and that we have to join hands and take immediate and definitive steps to prevent and optimally manage the risk factors associated with these pandemics. This can only be done by empowering both patients, and especially the primary care givers, who in many instances are the first, and often, the only medical personnel who a person has access to. Highly academic guidelines dictated by a few people are not the way forward. We need to be inclusive, take ground realities into consideration to help various regions and countries evolve the most optimal way forward. It would be better for the WHO consultation group to accept that, with the metabolic syndrome, we have a tool in our hands which can make both the treating physicians as well as the people aware of the need for early diagnosis and a comprehensive treatment of any, and all, risk factors for T2DM and ASCVD, and which would be "available, accessible and affordable" to most, if not all, people, rather than discard this as being "a premorbid condition of no clinical utility but just an exercise in futility".

Contents

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1. Who says lightning does not strike twice?

Whilst all innovations and new ideas will have their passionate proponents, one of the *sine qua non* of the medical world is that it will also have its opponents. The concept of the metabolic syndrome was no exception and went through its debates and controversies.

Soon after Reaven put forward his concept of Syndrome X [1], this was closely followed by many other definitions specifically those of the WHO [2], the European Group on Insulin Resistance (EGIR) [3], the NCEP (Adult Treatment Panel III) [4], the American Association of Clinical Endocrinologists (AACE) [5], American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) [6] and the International Diabetes Federation [7].

The AHA/NHLBI [6] and the IDF [7] definitions were in common use and although a significant amount of epidemiological data was generated, the use of either of these two definitions by different groups did create a problem in comparing data across studies and regions.

Recently, there was a harmonization between the two commonly used definitions [8] which is said to have ironed out the creases between the definitions of the metabolic syndrome especially the AHA/NHLBI [6] and the IDF [7] versions.

After the harmonization, the IDF has accepted that it would not ask for the presence of a predetermined waist measure as a *sine qua non* for the diagnosis and would accept a diagnosis of metabolic syndrome if any three of the five criteria were met. At the same time, it insisted on the use of ethnic- and country-specific criteria for waist measures even if this be only one of the five requirements. On its part, the AHA/NHLBI would recognize an increased risk for CVD and diabetes at waist circumference thresholds of $\geq$94 cms in men and $\geq$80 cms for women, and identify these as optional cutoff points for individuals or populations (Tables 1 and 2) [8].

In spite of the publication of this Interim report [8], arguments were made that it did not answer many of the key questions which had been raised by the ADA and the EASD [9,10], as well as some others [11–20], about the metabolic syndrome. Most of these have been answered repeatedly [21–29] and this statement [8] vehemently reiterates many of the arguments which have been made in defense of the metabolic syndrome in the past. One cannot keep answering queries *ad nauseum*!

But as has been said, "For those who believe, no proof is necessary. . . . for those who do not, no proof is enough!"

One would sincerely have hoped that we would now take a step forward and thrash out a consensus on the metabolic syndrome between the opponents and the proponents so that we could leave this controversy behind us and get on with our work which is to stem this rising pandemic of type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) [30].

2. But lightning does strike twice!

A WHO Expert Consultation Group came out with a report [32] which basically reiterated the old arguments, though in a more nuanced manner, which had been used by those opposing the concept of the metabolic syndrome from its initial stages. The end recommendation was the same, that the metabolic syndrome was basically a premorbid condition and that there were many questions which needed to be answered before one could accept it as a clinical entity in its own right. This should have been no real surprise as the Group included members who previously contested the metabolic syndrome concept for a variety of reasons [12,16–20]. Astoundingly, one author had been up to very recently amongst the leading proponents of the metabolic syndrome concept and its harmonization [7,8,21,23,30,31].

One of the prime objections which had been raised was an absence of a widely accepted consensus defining the criteria which make up the components of the metabolic syndrome. This, the Expert Consultation Group felt, added to the confusion as different workers used different definitions. Although the report did mention that this had been resolved to an extent [8]. Why then should one keep harping on this?

Table 1
Diagnostic criteria for metabolic syndrome [8]. Measure (any three of the five criteria below constitute a diagnosis of metabolic syndrome).

Measure	Categorical cut points
Central obesity	Population- and country-specific definitions
Raised triglycerides[a]	>150 mg/dL (1.7 mmol/l) or on specific treatment for this lipid disorder
Reduced HDL cholesterol[a]	<40 mg/dL (1.0 mmol/l) in men, <50 mg/dL (1.3 mmol/l) in women or on specific treatment for reduced HDL-C
Raised blood pressure	$\geq$130 mmHg systolic blood pressure or $\geq$85 mmHg diastolic blood pressure or on treatment for previously diagnosed hypertension
Elevated fasting plasma glucose	Fasting plasma glucose[b] $\geq$100 mg/dL (5.6 mmol/l) or on drug treatment for elevated glucose

HDL-C indicates high-density lipoprotein cholesterol.
It is recommended that IDF cutoff points be used for non-Europeans and either the IDF or AHA/NHLBI cutoff points be used for people of European origin until more data is available.
[a]The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High dose $n-3$ fatty acids presumes high triglycerides.
[b]Almost all patients with type 2 DM will have the metabolic syndrome by the proposed criteria.