EDITORIAL

The Metabolic Syndrome: Is the combination of three any better than the value of one, or two?

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INTRODUCTION

In this issue of *The Journal*, Chanda and co-authors [1] present data on the clinical utility of risk components of the metabolic syndrome (MetS) in predicting the presence of the syndrome in patients with Type 2 DM. The syndrome was highly prevalent, with 73% of the patients meeting its case definition. A large waist circumference (WC) was present in 68% of the study population, and predicted the presence of the MetS in a majority of them. Because of its simplicity in assessment compared to other components of the syndrome, the authors recommend use of WC as an initial screening test for MetS, especially in resource-poor settings.

But what is the metabolic syndrome? And why should we be concerned about it?

With renewed focus on non-communicable and lifestyle diseases around the world, greater efforts are needed for early recognition, intervention and public-health measures to reduce the burden of risk for chronic diseases. The MetS has been described among virtually all population groups around the globe, and there is only one message: it is not good for health! Understanding it, and knowing how to recognise it, thus, makes sense.

In this review, we look at how the case definition of the syndrome has evolved over the years, its prevalence and, ongoing controversies regarding whether diagnosis of the MetS adds any more value to estimates of prospective development of its attendant complications than what its components are able to predict.

BACKGROUND

The concept of metabolic syndrome (MetS) was first introduced by Reaven in 1988 [3]. The syndrome is a combination of medical conditions, which, when present in an individual, portends increased risk of development of type 2 diabetes mellitus (DM) and atherosclerotic cardiovascular disease (CVD). It is also known as **metabolic syndrome X**, **cardiometabolic syndrome**, **syndrome X**, **insulin resistance syndrome**, and **Reaven's syndrome** (named for Reaven).

Since its introduction into the medical literature, the MetS has excited a lot of research interest as well as debate. Various studies have documented the prevalence of the syndrome among diabetic and non-diabetic populations and evaluated its contribution to all-cause and cardiovascular (CV) mortality. However, debate still rages whether the syndrome is a distinct entity or simply reflects an aggregation of CVD risk factors. In this regard, opponents of the syndrome argue that identification of individual components of the syndrome is of greater clinical utility since these are associated with greater odds of prospective development of CVD disease and type 2 DM than diagnosis of the MetS [2].

DEFINITION

Over the years, the definitions of the MetS and cut-off points for its components have undergone progressive refinement. This has aided and facilitated both clinical and epidemiological research on the syndrome. There are at present, at least five sets of defining criteria for the MetS: the World Health Organisation (WHO) definition of 1999; The European Group for the Study of Insulin Resistance (EGIR) definition of 1999; The US National Cholesterol Education Program (NCEP) Expert Panel definition of 2001; the International Diabetes Federation (IDF) Consensus worldwide definition of 2006; and the harmonised / unified definition of 2010.

The WHO definition

In the quest to establish a uniform definition for the syndrome and, thus, a basis for comparison between studies, the World Health Organisation (WHO) issued the first working definition of MetS [4]. In the WHO definition, MetS was defined as insulin resistance (measured by clamp studies) or impaired glucose regulation (impaired fasting blood sugar, impaired glucose tolerance, or type 2 diabetes mellitus) with 2 or more of the following: 1) a Blood Pressure (BP) of 140 / 90 mm Hg or higher; (2) triglyceride levels of 1.7 mmol/L or higher and / or High Density Lipoprotein Cholesterol (HDL-C) levels less than 0.9 mmol/L in men and less than 1.0 mmol/L in women; (3) waist-hip ratio greater than 0.90 in men and greater than 0.85 in women and /or body mass index

(BMI) greater than 30; or (4) microalbuminuria (urinary albumin excretion ratio ≥ 20 µg/min or albumin : creatinine ratio ≥30 mg/g).

The EGIR definition

The European Group for the Study of Insulin Resistance (EGIR) proposed several modifications to the WHO working definition for the diagnosis of the MetS in non-diabetic individuals [5]. The proposed modifications aimed to focus attention on criteria that are applicable in epidemiologic research and clinical practice. Thus, the EGIR proposed use of fasting plasma insulin as a surrogate for insulin resistance instead of the euglycemic hyper-insulinemic clamp technique used in the WHO criteria. Secondly, the EGIR recommended use of fasting plasma glucose (≥6.1 mmol/L) instead of oral glucose tolerance. The EGIR also recommended a change in definition of dyslipidemia to triglyceride level higher than 2.0mmol/L and/ or HDL-C level less than 1.0 mmol/L in both men and women; use of waist circumference (≥94 cm in men and ≥80 cm in women) instead of waist – hip ratio; and omission of BMI and microalbuminuria from the definition.

The NCEP Definition

The third set of diagnostic criteria was issued by the National Cholesterol Education Program (NCEP) Expert Panel [6]. The NCEP criteria omit the presence of insulin resistance and are based on the presence of 3 or more of five components: 1) A BP of 130/ 85 mm Hg or greater; 2) Fasting plasma glucose concentration higher than 6.1mmol/L; 3) triglyceride concentration of 1.69 mmol/L or greater; 4) HDL-C concentration less than 1.04 mmol /L; and [5] waist circumference greater than 102 cm in men and 88 cm in women. The NCEP criteria were more tailored for clinical use.

The IDF definition

In 2006, the International Diabetes Federation (IDF) issued what they called 'The IDF Consensus worldwide definition of the metabolic'[7]. The definition emphasised the importance of central obesity with recognition of ethnic variations in waist size. According to the IDF definition, a person is deemed to have the MetS if they have central obesity (defined as increased waist circumference with ethnic specific values) plus any two of four other components: 1) raised triglycerides (≥1.7 mmol/L); 2) reduced HDL-C (< 1.03 mmol/L in men and (< 1.29 mmol/L in women); 3) raised blood pressure (systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg, or treatment for previously diagnosed hypertension); and 4) raised fasting plasma glucose (FPG ≥5.6 mmol/L). There is a general proviso that *If body mass index (BMI) is >30kg/m², central obesity can be assumed and waist circumference does not need to be measured.*

The IDF criteria identified three main ethnic specific cut-off values for waist circumference. These are ≥102 cm and ≥88 cm for American men and women, respectively; ≥94 cm and ≥80 cm for men and women of European descent, respectively; ≥90 cm and ≥80 cm for men and women, respectively of South Asian, Chinese and Japanese descent. For Sub-Saharan Africans, Eastern Mediterranean and Middle East (Arab) populations, the IDF recommend using the European waist circumference cut-off values until more data becomes available while for ethnic South and North Americans, the IDF criteria recommend use of the South Asian cut-off values.

The harmonised definition of 2010

Over the years, The IDF definition and the [**National Cholesterol Education Program Adult Treatment Panel**] ATP III definition have been the two that have been utilized most frequently. However, as more data has become available, the definition of the MetS has continued to be refined in the quest for a globally accepted definition. More recently, different organisations comprising the **International Diabetes Federation** (IDF), the **National Heart, Lung, and Blood Institute** (NHLBI), the **World Heart Federation**, the **International Atherosclerosis Society**, and the **American Heart Association** (AHA) signed to a single definition of the MetS [8]. This is a further attempt to eliminate some of the confusion regarding how to identify patients with the syndrome. In particular, the streamlined criteria address differences in the previous IDF and the ATP III definitions of what constituted abdominal obesity as defined by measurements in waist circumference. Now, the criteria for elevated waist circumference are based on population- and country-specific definitions.

Further, the IDF previously considered elevations in waist circumference mandatory when defining metabolic syndrome, while the ATP III did not. In the harmonised / streamlined definition, waist circumference is just one of five criteria that one can use when diagnosing the metabolic syndrome. Patients with three of the five criteria, including elevated waist circumference, elevated triglycerides, reduced HDL-cholesterol levels, elevated blood pressure, and elevated fasting-glucose levels, are considered to have the syndrome. The full criterion set of the unified / streamlined definition of MetS is shown in table 1.

Table 1: 2010 Harmonised Criteria for Clinical Diagnosis of the Metabolic Syndrome

Component	Categorical cut points
Elevated waist circumference	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	≥1.7 mmol/L (≥150 mg/dL)
Reduced HDL cholesterol (drug treatment for reduced HDL cholesterol is an alternate indicator)	< 1.03 mmol/L in (<40 mg/dL) for males and < 1.29 mmol/L (<50 mg/dL) for females
Elevated blood pressure (drug treatment for elevat ed blood pressure is an alternate indicator)	Systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg
Elevated fasting glucose (drug treatment for elevated glucose is an alternate indicator)	≥5.6 mmol/L (≥100 mg/dL)

PREVALENCE

Life style and dietary habits play a significant role in predisposing to development of the MetS. Well-known risk factors include mental stress, over-weight and obesity, a sedentary life style with low physical activity and high caloric intake, and aging. In a number of studies among the general population in the Western world, the prevalence of MetS has varied between 15% and 30% (9 - 11). Across all population groups, the syndrome prevalence is higher among women and increases with age.

Some disease states carry a particularly high risk of the syndrome. For example, the large majority (approximately 75%) of patients with type 2 DM or impaired glucose tolerances, and 50% of patients with coronary heart disease, have MetS [12]. Other non-communicable disease conditions that carry a high risk of the MetS are lipodystrophic disorders, both genetic and acquired (such as HIV- related lipodystrophy in patients on Highly Active Antiretroviral Therapy) [12], **Schizophrenia and other psychiatric illnesses [13, 14], and some rheumatic disorders such as psoriatic arthritis [15].**

THE ONGOING DEBATE

Years after the term *metabolic syndrome* was first coined, controversy continues over the clinical utility and validity of the syndrome. The argument over relevance of the MetS has set part of the diabetes community against some of those in cardiology. On one hand, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) are opposed to the use of the term MetS while, on the other hand, the National Heart, Lung and Blood Institute (NHLBI) and the American Heart Association (AHA) encourage use of the MetS concept [16, 17].

Proponents of the MetS argue that the concept is valid in that it enables clinicians identify people with this constellation of risk factors whom they could then target for more aggressive lifestyle advice. Some point out that the MetS is particularly applicable in the primary-care setting, where recognition of the clustering of risk factors can enable a doctor to make the patient more aware of the importance of lifestyle changes [18].

Opponents of the syndrome argue that diagnosis of the MetS does not add any more value to risk prediction than its individual components. Therefore, they see no additional benefit from identifying these clusters of risk factors over measuring and treating the individual risk factors [18, 19].

Both sides of the argument have compelling supportive evidence. Here is some of that evidence.

Evidence against

Several studies have shown that presence of the syndrome in an individual is no more predictive of prospective development of CVD or type 2 DM than individual components of the syndrome. In this regard, an analysis of two prospective studies by Sattar et al., found that the MetS was not associated with cardiovascular (CV) risk in the elderly although it was associated with risk of diabetes [20].

However, the study revealed that impaired fasting blood glucose alone was as strong an indicator of incident diabetes as the syndrome. Thus, the authors conclude that metabolic syndrome is not necessary to identify those at risk of diabetes either.

Included in this study were participants of 2 prospective trials: the **Prospective Study of Pravastatin in the Elderly at Risk** (PROSPER) trial, with 4812 nondiabetic men and women aged 72 to 82 years who were followed up for 3.2 years, and the **British Regional Heart Study** (BRHS), with 2737 nondiabetic men aged 60 to 79 years, followed up for 20 years.

One of the shortcomings of trying to use the MetS as a predictive tool has recently been highlighted in an analysis to show how information loss occurs during data transformation when multiple continuous biological variables are dichotomized [21]. Using the metabolic syndrome as a case in point, the authors demonstrate that transforming the multiple MetS components into a single dichotomous indicator discarded over 98% of the potential information contained in the original measurements. This is food for thought.

However, the original concept of MetS was not to be a diagnostic or prognostic tool.

In 1977 and 1978, Gerald B. Phillips developed the concept that risk factors for MI aggregate in some individuals to form a "constellation of abnormalities" comprising hypertension, glucose intolerance, hyperinsulinemia, hypercholesterolemia and hypertriglyceridemia. It was notable that these abnormalities were not only associated with heart disease

but also with aging, overweight and obesity, and other clinical conditions. From an epidemiology viewpoint, it was of great interest to investigate whether these conditions had a single underling cause, the identification of which could lead to the prevention of cardiovascular disease; Phillips hypothesized that this factor was sex hormones [22].

In 1988, Gerald M Reaven proposed insulin resistance as the underlying factors [3].

Thereafter, the syndrome started to be used as a diagnostic tool and arguments ensued. Nevertheless, in recent years, new data has emerged which appears to support use of the MetS as a predictive tool.

Evidence in support of the MetS

In a meta-analysis that included 87 studies, with 951 083 patients, Mottillo et al., showed that patients with metabolic syndrome had an approximate twofold increase in risk of CVD, cardiovascular mortality, myocardial infarction (MI), and stroke and a 1.5-fold increase in risk of all-cause mortality [23]. This is the first meta-analysis to establish the cardiovascular risk associated with the MetS as defined by the 2004 revised NCEP ATP III criteria of the syndrome.

In another study, an observational longitudinal cohort study of 25,471 Japanese men aged 20–61 years with a median follow-up of 7.5 years showed that MetS (defined by a modified definition of MetS from the Japanese Society of Internal Medicine and the NCEP ATPIII) associated with increased rates of all-cause mortality, Ischemic heart disease (IHD) and CVD. The study also demonstrated that any combination of three of the MetS components associated with significant increases in rates of all-cause mortality and IHD while hypertension in combination with dyslipidaemia associated with higher rates of CVD (24).

SHOULD WE BE LOOKING OUT FOR AND DIAGNOSING THE MetS?

With all this apparent confusion surrounding the MetS, what is the bottom-line? Should we, in our practices, endeavour to diagnose the syndrome or be content with identifying and treating individual risk components? The important message here is that risk factors for CVD and type 2 DM do aggregate in some individuals. Recognising them is paramount, and that should be our first concern.

USEFULNESS OF ALGORITHMS IN CLINICAL DECISION-MAKING

Availability of simple and easily adaptable clinical diagnostic algorithms for identifying people with the greatest odds of having the syndrome is one step towards provision of cost-effective care as it enriches clinical decision-making. In this scenario, resources for expensive tests (if they cannot be avoided completely) are reserved for the further evaluation of only those with the greatest probability of having the syndrome.

Accurate clinical decision making requires, among many other factors, an ability to estimate probability of disease or prognosis given a particular clinical scenario (history and findings of a physical examination). This estimate, termed the “pre-test probability”, is modified by the results of diagnostic tests to arrive at a “post-test probability” of disease.

In this respect, the information we get from Chanda et al's findings is like this: the prevalence of MetS among Zambian type 2 diabetics is 73%. Before assessing the patient further for other components of the syndrome, this (73% or 0.73), is the “pre-test probability” that the patient has MetS. Once we have carried out further tests, we can estimate the “post-test probability” of the syndrome. When the patient also has hypertension, the likelihood that they have the MetS rises from 0.73 to 0.85; and to 0.96 or 0.97 if they also have increased waist circumference or have low HDL cholesterol, respectively.

As to which test one should chose, depends on the prevalence of the condition under scrutiny in the target population as this affects the sensitivity (proportion of individuals with an attribute that the test correctly identifies) and specificity (proportion of individuals without an attribute that the test correctly identifies) of the test.

Again, looking through Chanda et al's results, low HDL and raised triglycerides are associated with “post-test probabilities” of MetS as high as that of increased waist circumference. However, owing to their low prevalence among the study population (and by inference, Zambian type 2 diabetics in general), screening algorithms based on low HDL cholesterol or raised triglycerides would miss the diagnosis on many patients with MetS. In this regard, the low HDL cholesterol or raised triglycerides 'tests' would only correctly identify 28% and 42% of patients with the MetS, respectively. Thus, they would have very high false negative rates of 72% and 58%, respectively. On the other hand, screening algorithms based on a large waist circumference would correctly identify 90% of patients with the MetS; a false negative rate of only 10%. This is what makes it a more attractive screening test than the other components.

Therefore, for patients with type 2 DM, we have a simple screening tool that should enable us identify those with higher likelihood of having the MetS, and target them for more intensive lifestyle education and counselling. This can be incorporated into routine clinic patient assessment guidelines easily and at very minimal cost.

REFERENCES

1. H Chanda, P Kelly, B Andrews, S Siziya & S Lakhi. Predictive value of Metabolic Syndrome components in detecting the syndrome in patients with type 2 Diabetes Mellitus. *Med J Zambia* 2010; 37 (3):
2. Sattar N, McConnachie A, Shaper AG, et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. *Lancet* 2008; 371 (9628): 1927 – 1935.
3. Reaven GM. Banting Lecture 1988: role of insulin resistance in human disease. Diabetes 1988; 37: 1595 – 1607).
4. Alberti K, Zimmet P, for a WHO Consultation. Diagnostic and Classification of Diabetes Mellitus. Geneva, Swizerland: World Health Organisation; 1999. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1.
5. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation: European Group for the Study of Insulin Resistance (EGIR). Diabet Med. 1999; 16: 442 – 443.
6. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486 – 2497.
7. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome-a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006; 23(5): 469-80
8. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome. A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120:1640-1645.
9. Yong- Woo Park, Shankuan Zhu, Latha Palaniappan, et al. The Metabolic Syndrome: Prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988 – 1994. Arch Intern Med 2003; 163: 427 – 436.
10. Gang Hu, Qing Qiao, Jaakko Tuomilehto, Beverly Balkan, Knut Borch-Johnsen & Kalevi Pyorala; fot the DECODE study Group. Prevalence of the metabolic syndrome and its relation to All-Cause Cardiovascular Mortality inNodiabetic European Men and Women. Arch Intern Med 2004; 164: 1066 – 1076.
11. Riedier ND, Clara I, Prevalence of metabolic syndrome in the Canadian adult population. CMAJ 2011; Available at: http://www.cmaj.ca.
12. Fauci, Anthony S. (2008). *Harrison's principles of internal medicine*. McGraw-Hill Medical.
13. John, A. P.; Koloth, R.; Dragovic, M.; Lim, S. C. (2009). "Prevalence of metabolic syndrome among Australians with severe mental illness". *The Medical journal of Australia* 190 (4): 176–179.
14. Narasimhan M, Raynor JD. Evidence-based perspective on metabolic syndrome and use of antipsychotics. Drug Benefit Trends. 2010; 22:77 - 88.
15. Quilon A III, Brent L. The primary care physician's guide to inflammatory arthritis: diagnosis. J Musculoskel Med. 2010;27: 223-231.
16. Richard Kahn, John Buse, Ele Ferrannini, & Michael Stern. The Metabolic Syndrome: Time for a Critical Appraisal; Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005; 28:2289–2304.
17. Scott M. Grundy, H. Bryan Brewer, Jr, James I. Cleeman, Sidney C. Smith, Jr and Claude Lenfant. Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation* 2004, 109:433-438
18. Sue Hughes. Arguments continue over the metabolic syndrome. The heart.org July, 2010. Available at http://www.theheart.org
19. Kahn R. Metabolic syndrome – what is the clinical usefulness? *Lancet* 2008 doi: 10.1016/S0140-6736 (08) 60731-X
20. Sattar N, McConnachie A, Shaper AG et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. *Lancet* 2008 doi: 10.1016/S0140-6736 (08) 60602 -9
21. Jason W. Beckstead & Theresa M Beckie. How Much Information Can Metabolic Syndrome Provide? An Application of Information Theory. Med Decis Making, 2011; 31(1): 79-92
22. Phillips GB. "Sex hormones, risk factors and cardiovascular disease." *The American journal of medicine*, 1978; 65 (1): 7–11.
23. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk. A systematic review and meta-analysis. *J Am Coll Cardio*l 2010; 56:1113-1132.
24. Takahisa Kondo, Shigeki Osugi, Keiko Shimokata, et al. Metabolic syndrome and all-cause mortality, cardiac events, and cardiovascular events: a follow-up study in 25,471 young- and middle-aged Japanese men. *European Journal of Cardiovascular Prevention &* Rehabilitation August 2011 vol. 18 no. 4 574-580.