Metabolic syndrome under fire: Weighing in on the truth

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In the past two decades, the 'metabolic syndrome' has raised much clinical and research interest and remains a controversial topic. The constellation of commonly coexisting cardiovascular risk factors, now known as the metabolic syndrome, has had many definitions which has added to the confusion surrounding the syndrome. Recently, the controversy has been escalated by a joint statement from the American Diabetes Association and the European Association for the Study of Diabetes calling into question the existence and clinical utility of the metabolic syndrome as a discrete clinical entity. Despite the controversy, there is agreement that the risk factors of abdominal obesity, hypertension, elevated glucose and dyslipidemia commonly coexist in the same patient, and are important to identify when assessing an individual patient's risk. Therefore, whether the 'syndrome' is a distinct clinical entity is not important. By definition, a syndrome is a group of signs or symptoms that commonly group together. It remains a useful clinical tool to raise awareness among health care professionals to look for 'nontraditional' cardiovascular risk factors, such as glucose intolerance or elevated waist circumference, in patients with other components of the syndrome, without negating the importance of identifying and treating the other 'traditional' risk factors not identified in the syndrome. It also reminds clinicians of the importance of lifestyle interventions to treat all of the components of the syndrome. Therefore, the 'metabolic syndrome' continues to serve a useful clinical purpose to raise awareness among health care professionals and aid in identifying high-risk individuals.

Key Words: Cardiovascular risk assessment; Metabolic syndrome

CLINICAL CONTEXT

The metabolic syndrome is typically described as a constellation of metabolic abnormalities associated with an increased risk of cardiovascular disease (CVD) and type II diabetes mellitus (DM) (1). Over the past two decades, many other names have been given for this constellation, including 'insulin resistance syndrome', 'syndrome X' and 'the deadly quartet'. There has also been an abundance of differing diagnostic criteria that have been developed by various organizations around the world. To add to the confusion, a recent joint statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) has called into question the existence and validity of the metabolic syndrome as a discrete clinical entity (2). In an attempt to shed some light on the situation, the present article describes the historical

Le syndrome métabolique dans la ligne de mire : Question de poids et de mesure

Depuis une vingtaine d'années, le « syndrome métabolique » suscite beaucoup d'intérêt dans le milieu clinique comme en recherche et ce sujet reste controversé. La coexistence fréquente d'une constellation de facteurs de risque cardiovasculaires, généralement désignée par le terme syndrome métabolique, a été définie de plusieurs façons, ce qui a quelque peu contribué à la confusion qui l'entoure. Or, la controverse a récemment été ravivée par la position conjointe de l'*American Diabetes Association* et de l'Association européenne pour l'étude du diabète qui remettent en question la pertinence clinique, voire l'existence du syndrome en tant qu'entité clinique distincte. Au-delà de la controverse, on s'entend sur le fait que les facteurs de risque que sont l'obésité abdominale, l'hypertension, l'hyperglycémie et la dyslipidémie affectent souvent simultanément certains patients et que ce sont d'importants indicateurs de la nécessité d'évaluer le risque individuel global. Il devient ainsi secondaire de savoir si le syndrome est ou non une entité clinique distincte. Un syndrome est essentiellement un ensemble de signes ou symptômes regroupés. Cette notion reste utile sur le plan clinique pour éveiller les soupçons des professionnels de la santé vis-à-vis de certains facteurs de risque non traditionnels à surveiller, comme l'intolérance au glucose et le tour de taille excessif chez des patients qui présentent déjà d'autres éléments du syndrome, sans pour autant nier l'importance du dépistage et de la prise en charge des autres facteurs de risques « traditionnels », moins couramment liés au syndrome. La notion rappelle en outre aux cliniciens l'importance des interventions non pharmacologiques pour en traiter tous les éléments. Par conséquent, le terme « syndrome métabolique » reste pertinent comme outil clinique pour attirer l'attention des professionnels de la santé et pour identifier les sujets à risque.

background, reviews the most commonly used clinical criteria, discusses the controversy surrounding the existence of the metabolic syndrome and concludes with the authors' viewpoints on the syndrome's clinical utility.

HISTORICAL BACKGROUND

The metabolic syndrome, like many things in medicine, represents a 'rediscovery' of descriptions from long ago. The earliest description of an association of certain metabolic abnormalities, namely hyperlipidemia, obesity, bleeding tendency and saturated fat ingestion, as well as its successful dietary treatment, dates back to the 17th century (3). In the 19th century, Mogagni (3) described an association between visceral obesity, hypertension, bladder stones and atherosclerosis. During the 1940s and 1950s, Jean Vague (4) published a series of papers

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TABLE 1
World Health Organization clinical criteria for the metabolic syndrome

Insulin resistance, defined by one of the following:

- Type II diabetes mellitus
- Impaired fasting glucose (fasting plasma glucose of 6.1 mmol/L or greater)
- Impaired glucose tolerance (2 h postprandial glucose of 7.8 mmol/L or greater)
- Glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions (for those with normal fasting glucose levels)

Plus two of the following:

- High blood pressure (systolic 140 mmHg or higher, or diastolic 90 mmHg or higher) and/or antihypertensive medication
- Plasma triglyceride concentration of 1.7 mmol/L or higher
- High-density lipoprotein cholesterol less than 0.9 mmol/L in men or less than 1.0 mmol/L in women
- Body mass index greater than 30 kg/m² and/or waist to hip ratio greater than 0.9 in men or greater than 0.85 in women
- Urinary albumin excretion rate of 20 µg/min or greater, or albumin to creatinine ratio of 30 mg/g or greater

Adapted from reference 7

TABLE 2
National Cholesterol Education Program Adult Treatment Panel III clinical criteria for identification of the metabolic syndrome

Three or more of the following:

- Abdominal obesity (waist circumference measurement)
Men: greater than 102 cm
Women: greater than 88 cm
- Triglyceride concentration of 1.7 mmol/L or higher
- High-density lipoprotein cholesterol concentration
Men: less than 1.03 mmol/L
Women: less than 1.30 mmol/L
- Blood pressure 130/85 mmHg or higher
- Fasting glucose of 5.6 mmol/L or higher

Adapted from references 1 and 8

relating the importance of body fat distribution to the risk of both CVD and DM. In 1965, at the first meeting of the EASD, Avogaro et al (5) presented the first systematic description of a syndrome involving hyperlipidemia, obesity, DM, ischemic heart disease and arterial hypertension. Then, in 1988, Reaven (6) introduced what he termed 'syndrome X' in his Banting Lecture at the ADA meeting. This was described as a clustering of disturbances in glucose and insulin metabolism, dyslipidemia and hypertension with insulin resistance/hyperinsulinemia as a critical underlying factor representing an important cardiovascular risk factor. This clustering was subsequently called the 'insulin resistance syndrome' and even 'Reaven's syndrome'. 'Metabolic syndrome' is the currently accepted term, and the most widely used clinical criteria come from the World Health Organization (WHO) (Table 1) (7), the Third Report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (Table 2) (1,8) and, most recently, the International Diabetes Federation (IDF) (Table 3) (9,10).

CLINICAL CRITERIA FOR THE METABOLIC SYNDROME

WHO (1998)

A consultation group was organized by the WHO in 1998 to describe and define the metabolic syndrome (7). The primary

TABLE 3
International Diabetes Federation consensus definition of the metabolic syndrome

Definition of metabolic syndrome

Central adiposity (waist circumference, cm)	Men	Women
Europid*	≥94	≥80
South Asian†	≥90	≥80
Chinese	≥90	≥80
Japanese	≥85	≥90

Plus any two of the following:

- Triglyceride concentration of 1.7 mmol/L or higher
- High-density lipoprotein less than 0.9 mmol/L for men, or less than 1.1 mmol/L for women
- Blood pressure (systolic 130 mmHg or greater, or diastolic 85 mmHg or greater) or antihypertensive treatment
- Fasting plasma glucose of 5.6 mmol/L or greater, or pre-existing diabetes, or impaired glucose tolerance

*Europid criteria for individuals of European, sub-Saharan African or Middle Eastern descent; †South Asian criteria for individuals of South Asian, South or Central American descent. Adapted from references 3 and 4

consequence of the metabolic syndrome is CVD. Insulin resistance (IR) was felt to be the most important underlying factor and, therefore, a necessary component of the syndrome. IR was defined as the presence of type II DM, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or lowered insulin sensitivity measured under hyperinsulinemic and euglycemic conditions. In addition to IR, at least two other components were needed to diagnose metabolic syndrome (hypertension, obesity [measured by body mass index or waist-to-hip ratio], hypertriglyceridemia, low high density lipoprotein [HDL] or microalbuminuria). Other identified parts of the metabolic syndrome included hyperuricemia, hypercoagulability and hyperleptinemia, but these were not required.

NCEP ATP III (2001)

The NCEP ATP III report also recognized the metabolic syndrome as a major risk factor for CVD (1) but the precise clinical criteria differed from those of the WHO. Six components were described that related to CVD: abdominal obesity; atherogenic dyslipidemia; raised blood pressure; IR with or without glucose intolerance; proinflammatory state; and prothrombotic state. Obesity, abnormal fat distribution, IR and other factors (age, genetics and hormonal changes) were discussed as possible players in the pathogenesis of metabolic syndrome, but no definite conclusions were drawn. The actual clinical criteria are shown in Table 2. At least three of the five listed characteristics were required. These characteristics included abdominal obesity measured by waist circumference, hypertension, hypertriglyceridemia, low HDL and raised plasma glucose. The presence of type II DM did not exclude the diagnosis of metabolic syndrome. This definition differed from the WHO definition in that IR was not a necessary component, although the assumption was made that the vast majority of patients who met the criteria would have IR. Also, a glucose tolerance test or 2 h postprandial glucose value was perceived to be clinically impractical. Thus, an abnormality in the fasting glucose level was felt to be sufficient to demonstrate glucose intolerance. Most recently, the fasting glucose threshold was modified and reduced to 5.6 mmol/L to reflect the modified definition of IFG proposed by the ADA (8).

IDF consensus (2005)

As of 2004, there were at least four different sets of published criteria for the metabolic syndrome. Given the lack of universally accepted criteria, the IDF convened an international group in May 2004 to establish yet another working diagnostic tool for the metabolic syndrome that could identify individuals at high risk of developing CVD and DM. In April 2005, the consensus definition was presented in Berlin at the First International Congress on 'Prediabetes' and the Metabolic Syndrome – Epidemiology, Management and Prevention of Diabetes and Cardiovascular Disease (9,10) (Table 3). The key components were central adiposity, dyslipidemia, hypertension and dysglycemia.

'Central adiposity', assessed clinically by an increased waist circumference, was determined to be an absolute necessity for the syndrome due to its strong correlation with the other features of the metabolic syndrome and its probable role in the pathogenesis of the metabolic abnormalities. Previous criteria for the metabolic syndrome suggested waist circumference thresholds for men and women that were supposed to be applied universally, regardless of ethnicity. However, it was evident that metabolic abnormalities were present in individuals of certain ethnicities at much lower waist circumferences (11). Thus, the IDF definition proposed ethnicity-specific waist circumference values, identifying four major ethnic groupings based on best available data: Europid (defined in Table 3), South Asian, Chinese and Japanese.

In addition to central adiposity, individuals required two or more of the following: hypertriglyceridemia, low HDL, increased blood pressure and glucose intolerance (IFG, IGT or DM). Unlike the WHO definition, IR was not specifically identified because it was felt that central obesity plus hypertriglyceridemia were sufficiently adequate surrogates for IR.

THE CONTROVERSY

In September 2005, the ADA and EASD published a joint statement calling into question the existence of metabolic syndrome, as defined by the NCEP and the WHO, as a clinical entity based on their interpretation of the available evidence (2). A number of concerns were raised regarding the current descriptions of the syndrome. These concerns included ambiguous criteria with ill-defined threshold values; questionable value of including DM in the definition because DM is already known to be a very significant risk factor for CVD; uncertainty of IR as the unifying etiology; lack of basis for including or excluding other CVD risk factors; variability of CVD risk dependent on the specific risk factor present; no additional CVD risk associated with the 'metabolic syndrome' compared with the sum of its parts; no difference between treatment of the 'syndrome' and the treatment of the individual components; and unclear medical value of diagnosing the 'syndrome'. Therefore, the ADA and EASD concluded that clinicians should no longer rely on, or look for, the presence of the 'metabolic syndrome' as a clinical entity and should concentrate their efforts on identifying and treating the individual CVD risk factors. This statement added to the existing confusion regarding the metabolic syndrome, previously generated by the multiple clinical criteria, and somewhat inconsistent study results and incompatibility of studies. Within a month of the publication of this statement, the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) published a joint statement supporting

the existence of the metabolic syndrome and the NCEP ATP III definition (8), and the IDF also published their summary of the consensus criteria and support for the existence of the metabolic syndrome as an important clinical entity (10).

INTERPRETATION

The ADA/EASD joint statement, AHA/NHLBI joint statement and IDF publication were all published within one month of each other in four different European and North American high-impact scientific journals. This obviously regenerated a lot of attention focusing on the existence and clinical importance of the metabolic syndrome. Interestingly, what has often been ignored in the 'controversy' is that the statements from the various organizations agreed with each other more than they differed.

The ADA/EASD statement suggests that the metabolic syndrome should not be considered a clinical entity because the underlying etiology is unknown and the criteria are imprecise. This point is actually acknowledged by the other organizations. The AHA, NHLBI and IDF agree that the metabolic syndrome should not be considered a discrete clinical entity and acknowledge that the underlying etiology is unclear. A syndrome, as defined by the Oxford English Dictionary, is 'a group of symptoms or signs that consistently occur together' (12). Based on this definition, the current definitions of metabolic syndrome qualify as a 'syndrome'. All of the groups basically acknowledge that the various components of the metabolic syndrome often do occur in the same patient. Furthermore, it is important to note that the various published criteria (WHO, NCEP, IDF, etc) are all consistent in their definition of the syndrome in that they all agree on a conceptual definition that includes an atherogenic dyslipidemia, IR/glucose intolerance, a proinflammatory and prothrombotic profile, and raised blood pressure. The differences in opinion between the groups are related to the clinical criteria used to identify patients with the syndrome. It is certainly true that many of the criteria are imprecise, a fact acknowledged by the various organizations. Over the years, a number of studies have been performed regarding the prevalence of the metabolic syndrome and its associated cardiovascular risk; however, the existence of multiple clinical criteria has made it difficult to compare studies and, therefore, precise thresholds have not been established. Many of the proposed thresholds are based on best available evidence or, in some cases, are arbitrary. However, this may be a necessary intermediate step to improve ease of clinical utility and, more importantly, to create a framework from which future research can be performed in an attempt to verify or redefine the thresholds. None of the existing definitions claim to be perfect, precise or definitive. As with many diagnostic criteria in medicine, they will continue to be subject to change and redefinition.

Finally, and perhaps most importantly, the clinical utility of the metabolic syndrome was also called into question. The main purpose of identifying the metabolic syndrome is to help physicians, and especially those in primary care, to identify patients at high risk of developing CVD or DM. All of the groups acknowledge that each component of the metabolic syndrome represents a significant risk factor. However, it remains controversial as to whether the 'syndrome' itself represents a higher cardiovascular risk than the sum of the risk factors themselves. Although this is certainly an important research question, it may not be a useful clinical distinction. If

one has more risk factors, one is at higher CVD risk. Current risk engines, such as the Framingham risk score, have issues of their own and high-risk patients are often missed because of their failure to incorporate both newer (eg, visceral fat, inflammation) as well as traditional (eg, family history of premature CVD) risk factors. Furthermore, most physicians do not routinely use such risk engines. Therefore, if the identification of a 'syndrome' helps clinicians to recognize a high-risk patient and remember to assess nonclassical CVD risk factors, such as IFG or IGT or elevated waist circumference, and then institute appropriate therapies (often lifestyle) targeting these risk factors, then the definition has served its clinical utility. The existence of the syndrome does not preclude the search for the other classical CVD risk factors, such as smoking and family history. These other risk factors remain important components of the assessment for a patient's overall CVD risk. Perhaps the clinical utility of the metabolic syndrome definition is its ability to raise awareness among clinicians to identify nontraditional risk factors for CVD that also warrant therapy, and not whether it can identify at-risk patients better than existing models.

The definition of the metabolic syndrome has served another important clinical purpose. It has raised awareness of the differences in cardiovascular risk factors in various ethnic populations and has sparked research into this important issue. When the initial definitions were applied to various populations around the world, it was discovered that they often underestimated CVD risk. Therefore, ethnicity-specific definitions have been proposed by the IDF. In addition to these ethnic differences, the identification and definition of the metabolic syndrome has generated a number of research hypotheses about its validity, predictive abilities and perhaps most importantly, its underlying etiologies. In that sense, the metabolic

syndrome as a clinical entity has served, and will likely continue to serve for many years, another important purpose.

CONCLUSIONS

Since Reaven's Banting lecture identifying the common clustering of CVD risk factors in the same patient and his proposal of an underlying etiology, there has been, and continues to be, much research and clinical interest in the metabolic syndrome. The multiple definitions and incompatibility of studies performed to date has generated much confusion. A recent joint statement from the ADA/EASD has generated even more controversy. However, despite the confusion, the metabolic syndrome still plays an important role in patient assessment. The clustering of CVD risk factors qualifies it as a syndrome. The existence of the components increases one's CVD risk. The metabolic syndrome has raised awareness among health care professionals to identify and initiate therapy for 'nontraditional' CVD risk factors, without negating the importance of identifying and treating the other traditional risk factors (eg, smoking, age, sex and family history). It has also raised questions about ethnic differences that had long been neglected. Therefore, if the identification of a 'syndrome' helps clinicians to recognize a high-risk patient and remember to assess nonclassical CVD risk factors, such as IFG, IGT or elevated waist circumference, then the definition has served its clinical utility. In addition, the 'syndrome' emphasizes the commonality of the various components, including their uniform response to lifestyle interventions of weight loss and physical activity, thereby further stressing the importance of lifestyle interventions. Therefore, the metabolic syndrome is an important clinical syndrome and should continue to be considered by clinicians and researchers.

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