

The Metabolic Syndrome: A Global Public Health Problem and A New Definition

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The constellation of metabolic abnormalities including centrally distributed obesity, decreased high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, elevated blood pressure (BP), and hyperglycaemia is known as the metabolic syndrome. Associated with a 3 fold and 2 fold increase in type 2 diabetes and cardiovascular disease (CVD), respectively, it is thought to be a driver of the modern day epidemics of diabetes and CVD and has become a major public health challenge around the world. Since its initial description, several definitions of the syndrome have emerged. Each of these definitions used differing sets of criteria, which reflected contrasting views on pathogenic mechanisms and the need for clinical usefulness. The use of these definitions to conduct research into the metabolic syndrome in diverse populations resulted in wide ranging prevalence rates, inconsistencies and confusion, and spurred on the vigorous debate regarding how the metabolic syndrome should be defined. In response to this controversy, the International Diabetes Federation (IDF) has recently proposed a new definition, which is applicable to populations around the world. It is envisaged that the development of the new definition for the metabolic syndrome will help resolve the confusion caused by the number of earlier attempts to define this important entity. *J Atheroscler Thromb*, 2005; 12: 295–300.

Key words: Obesity, Insulin resistance, Diabetes, Hypertension, Dyslipidaemia

Introduction

Over the last fifty years, there has been a dramatic change in the human environment, behaviours and way-of-life. These changes have resulted in escalating rates of both obesity and type 2 diabetes globally (2). Type 2 diabetes affects large numbers of people from a wide range of ethnic groups (2). It has been estimated that 190 million people worldwide have diabetes and it is very likely that this will increase to 324 million by 2025 (3). This epidemic, along with that for obesity, is taking place both in developed and developing nations and the com-

ination of obesity and diabetes is now recognised as one of the major threats to human health in the 21st Century.

Taking a global perspective, type 2 diabetes is responsible for over 90% of all cases of diabetes. Not only is the prevalence increasing, but the age of onset of type 2 diabetes is falling, and type 2 diabetes is now being reported in children and adolescents being diagnosed (4) in many countries, including Japan (5).

Type 2 Diabetes and the Metabolic Syndrome

Our understanding of type 2 diabetes and related disorders is undergoing a radical change. It was previously believed to be a relatively distinct disease entity, but in reality, type 2 diabetes and other categories of glucose intolerance are often part of a much broader underlying disorder characterised by the metabolic syndrome (6).

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Table 1. WHO, EGIR and ATPIII definitions of the metabolic syndrome.

WHO 1999	EGIR 1999	ATPIII 2001
Diabetes or impaired glucose tolerance or insulin resistance*	Insulin resistance* or hyperinsulinaemia (only non-diabetic subjects)	
Plus two or more of the following:	Plus two or more of the following:	Three or more of the following:
1. Obesity: BMI > 30 kg/m ² or WHR > 0.9 (M) > 0.85 (F)	1. Central obesity: Waist circumference ≥ 94 cm (M), ≥ 80 cm (F)	1. Central obesity: Waist circumference >102 cm (M), > 88 cm (F)
2. Dyslipidaemia: Triglycerides ≥ 150 mg/dl (1.7 mmol/l) or HDL-C < 35 mg/dl (0.9 mmol/l) (M) < 39 mg/dl (F) (1.0 mmol/l)	2. Dyslipidaemia: Triglycerides > 177 mg/dl (2.0 mmol/l) or HDL-C < 39 mg/dl (1.0 mmol/L)	2. Hypertriglyceridaemia: Triglycerides ≥ 150 mg/dl (1.7 mmol/l)
3. Hypertension: Blood pressure ≥ 140/90 mmHg or medication	3. Hypertension: Blood pressure ≥ 140/90 mmHg or medication	3. Low HDL -C: < 40 mg/dl (1.03 mmol/l) (M), < 1.29 mmol/l (50 mg/dl) (F)
4. Microalbuminuria: Albumin excretion ≥ 20 µg/min or albumin:creatinine ratio ≥ 30 mg/g	4. Fasting plasma glucose ≥ 110 mg/dl (6.1 mmol/l)	4. Hypertension: Blood pressure ≥ 130/85 mmHg or medication 5. Fasting plasma glucose ≥ 110 mg/dl (6.1 mmol/l)

* defined as the top quartile of fasting insulin in the non-diabetic population.

The metabolic syndrome is a constellation of CVD risk factors which apart from glucose intolerance (ie impaired glucose tolerance (IGT), impaired fasting glycaemia, (IFG) or diabetes) includes dyslipidaemia, hypertension, central obesity, insulin resistance, hyperinsulinaemia, and microalbuminuria (depending on which definition is used). This more contemporary view of type 2 diabetes also influences therapy for the disease. While the focus was previously on blood glucose control ('glucose-centricity'), there is evidence now for a far more aggressive approach to treat not just the hyperglycaemia but also other CVD risk factors such as hypertension, dyslipidaemia and obesity with the intent of significantly reducing cardiovascular morbidity and mortality (7, 8).

The Metabolic Syndrome - Its History

It was over 80 years ago that one of the first descriptions of the metabolic syndrome appeared. Kylin, a Swedish physician, described a clustering of hypertension, hyperglycaemia and gout (9). In 1947, Vague (10), in a landmark paper, reported that a particular obesity phenotype, upper body, android or male-type obesity, was associated with the metabolic abnormalities often seen with type 2 diabetes and with CVD. The clinical importance of the syndrome was highlighted some 40 years later by Reaven (11), who described the existence of a cluster of metabolic abnormalities, with insulin resistance

as the central pathophysiological feature, and labelled it 'Syndrome X'. Surprisingly, Reaven did not include obesity, a factor that has been linked with the metabolic syndrome in nearly all subsequent reports.

The metabolic syndrome has numerous names including The Deadly Quartet (12), Syndrome X (11) and the Insulin Resistance Syndrome (13). It is hoped that the term "metabolic syndrome" will now be used globally. In an attempt to achieve some agreement on definition, and to provide a tool for clinicians and researchers, a number of organisations formulated definitions (14–16). These were concordant in what are the essential components of the metabolic syndrome, glucose intolerance, obesity, hypertension and dyslipidaemia, but all differed in the details.

The first attempt at a global definition of the metabolic syndrome was by a World Health Organization (WHO) consultative group, and published in 1999 (14) (Table 1). Pivotal to the WHO definition was the biological and physiological description of insulin resistance (measured by the euglycaemic clamp). This definition was initially promoted as a working model, with the authors acknowledging that it should be improved on as new data came to light (15). Critics of the WHO definition identified several limitations, of which the most important related to the use of the euglycaemic clamp to measure insulin sensitivity, making the definition virtually impossible to use in either clinical practice or epidemiological studies.

Recognizing that the WHO definition might be too complex to apply in many settings, and as it relied heavily on insulin resistance, the European Group for the Study of Insulin Resistance (EGIR) developed a modified version of the WHO definition which would be easier to use as it relied on fasting insulin instead of the euglycaemic clamp to measure insulin resistance (17) (Table 1). The EGIR definition still retained insulin resistance as an essential component on the basis that they believed that insulin resistance was the underlying cause of the metabolic syndrome, but restricted the use of the definition to those in whom insulin resistance could be easily and reliably measured. Hence, people with diabetes were excluded from the definition, as the beta-cell dysfunction, characteristic of type 2 diabetes makes estimates of insulin sensitivity unreliable. The EGIR definition also introduced waist circumference EGIR (94 cm for men and 80cm for women) as the measure of adiposity and included modified cut points for the other components.

Two years later, the National Cholesterol Education Program of the USA introduced the ATP III definition (ATPIII) (16) (Table 1). Designed to have clinical utility, this definition did not include a specific measure of insulin sensitivity, and adopted a less ‘glucose-centric’ approach by treating all components with equal importance. Notably, it retained waist circumference as the measure of obesity (although with higher cut-points than EGIR (102 cm for men and 88 cm for women)). The ATPIII definition has been popular because of its simplicity in that its components are easily and routinely measured in most clinical and research settings. Unlike the WHO definition, the ATPIII definition did not incorporate inflammatory and haemostatic variables as part of an extended definition.

A modification of the ATPIII definition was also developed by the American Association of Clinical Endocrinology (AACE) based on the belief that insulin resistance was the core feature (17). The AACE listed four factors as ‘identifying abnormalities’ of the metabolic syndrome and these were elevated triglycerides, reduced HDL-C, elevated blood pressure, and elevated fasting and post load glucose. Factors such as obesity, diagnosis of hypertension, gestational diabetes or CVD or family history of diabetes, hypertension, non-European ancestry or age greater than 40 years and a sedentary lifestyle were listed as factors which increase the likelihood of the syndrome rather than as key identifying abnormalities. The AACE excluded obesity as a component as they viewed central obesity as a contributory factor in the development of insulin resistance rather than as a consequence. The omission of abdominal obesity as an identifying component in the AACE definition has evoked much criticism, especially in light of the growing evidence that it is a major risk factor for type 2 diabetes and cardiovascular disease (2, 18).

For these various metabolic syndrome definitions (14–

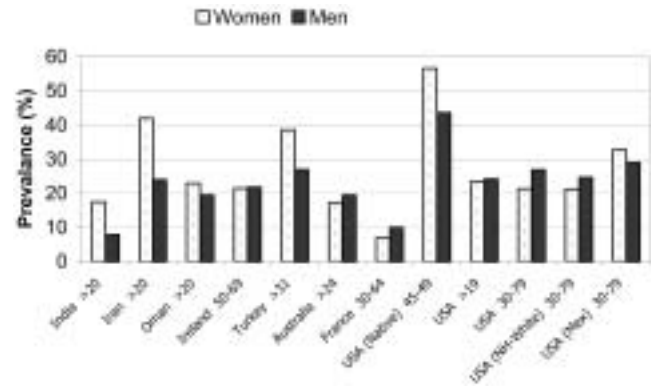


Fig. 1. The prevalence of the metabolic syndrome worldwide according to the ATP III definition (adapted from Cameron *et al.* (1)). Abbreviations: Mex, Mexican; NH, Non-Hispanics.

16), the cut-points for each component and the means of combining components differed. Given the obvious confusion between expert groups working in the area of metabolic syndrome, it is not surprising that clinicians were confused! Clinicians require simple tools to assess their patients and to improve patient management. In terms of simplicity, the ATPIII definition is superior requiring only a fasting assessment while the WHO definition may require an oral glucose tolerance test, and in addition, accurate measurement of insulin resistance requires a euglycaemic clamp.

A detailed review on the prevalence of the syndrome using different criteria has been published recently (1). However, comparisons of published prevalences for different populations are difficult despite attempts in recent years to reach agreement on the definition of the metabolic syndrome (7). There is an abundance of widely varying data, comparing prevalences using different criteria, which only serves to reinforce the need for a standardized definition internationally. These problems encouraged the IDF to introduce a new definition in an attempt to overcome these problems (19)

Prevalence estimates using ATPIII criteria from various countries are presented in Fig. 1. They differ with respect to the study design, sample selection, the year that they were conducted, the precise definition of the metabolic syndrome used and the age and sex structure of the population. Despite differences in the design of these studies and other variables mentioned above, certain observations can be made. For example, even for studies involving participants in the same age groups, there is a wide variation in prevalence in both genders. In those studies that include subjects 20–25 years and above, the prevalence varies in urban populations from 8% (India) to 24% (USA) in men, and from 7% (France) to 46% (Iran) in women. An interesting demonstration of the effect of

ethnicity on the metabolic syndrome is a comparison of the prevalence of the syndrome in the USA with lower prevalence in non-Hispanic Whites compared to Mexican Americans, and in African American men compared to Non-Hispanic White and Mexican American men (20).

A New Definition from the International Diabetes Federation

Clearly, the development of these metabolic syndrome definitions over the years has led to considerable confusion. The current definitions have not been 'user friendly' for clinicians and have contributed to an inability to accurately compare prevalences between populations. What was needed was a definition that was useful for clinicians identify which persons were at risk of type 2 diabetes and CVD and would facilitate epidemiological and clinical research into the metabolic syndrome.

In light of the controversy over the various limitations in the current definitions, the IDF decided that a more practical definition, which would be applicable globally for the identification of people at high risk of CVD, and diabetes, was urgently required (7, 19). A consensus group was formed comprising members of IDF from all regions and representatives from organisations including those who had contributed to the previous definitions. The primary aim of this group was to develop a new definition which would be clinically useful, facilitate the comparison of research into the metabolic syndrome across countries and populations, and highlight areas where more research was needed.

The IDF group recognized that central obesity was an important determinant of the metabolic syndrome, and that there is a strong association between waist circumference, CVD and other component of the metabolic syndrome (Table 2). In particular, visceral fat accumulation determined by CT scan has been demonstrated to have close correlation with the development of metabolic and cardiovascular diseases (21). Therefore, central obesity was placed in pivotal position of the new definition and an essential component.

The consensus group also placed particular emphasis on developing criteria for central obesity which would be appropriate for a wide variety of populations. Body mass index (BMI), though widely used, is not sufficiently sensitive to detect central obesity in different ethnic groups. Studies in Asia had demonstrated that the risk of type 2 diabetes and CVD for those with the metabolic syndrome is apparent at much lower levels of adiposity than in Europids (people of white European origin) (22). Further justification for ethnic-specific cut points came from a study in Asian Indians which showed that the risks of having type 2 diabetes increased significantly at a waist circumference of 85 cm in men and 80 cm in women (23). In addition, data from Japan had shown that cut-

Table 2. IDF Metabolic Syndrome World-wide Definition.

CENTRAL OBESITY
Waist circumference*– ethnicity specific (Table 2)
Plus any two of the following:
<ul style="list-style-type: none"> • RAISED TRIGLYCERIDES: <ul style="list-style-type: none"> ≥ 150mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality • REDUCED HDL-CHOLESTEROL <ul style="list-style-type: none"> < 40 mg/dl (1.03 mmol/l) in males < 50 mg/dl (1.29 mmol/l) in females or specific treatment for this lipid abnormality • RAISED BLOOD PRESSURE <ul style="list-style-type: none"> Systolic : ≥ 130 mmHg or Diastolic: ≥ 85 mmHg or treatment of previously diagnosed hypertension • RAISED FASTING PLASMA GLUCOSE** <ul style="list-style-type: none"> Fasting plasma glucose ≥ 100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes If above 5.6 mmol/l or 100 mg/dl, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

* If BMI is > 30 kg/m² then central obesity can be assumed, and waist circumference does not need to be measured. Ethnic specific waist circumference are listed in table 2.

** In clinical practice, IGT is also acceptable, but all reports of the prevalence of the metabolic syndrome should use only the fasting plasma glucose and presence of previously diagnosed diabetes to assess this criterion. Prevalences also incorporating the 2 hour glucose results can be added as supplementary findings.

points of 85 cm in men and 90 cm in women were more relevant to this community than were the ATP III criteria. The Japanese cut-points of waist circumference were determined by CT scan of visceral fat area (umbilical region). The number of risk factors including impaired glucose metabolism, lipid disorders and hypertension increased in both male and female subjects with visceral fat areas greater than 100 cm² (21). As a result, the IDF Consensus group have recommended cut points for central obesity based on waist circumference which are applicable to individual ethnic groups (Table 3).

It was also decided that the definition should be less 'glucose-centric' and the IDF definition has states of glucose intolerance in a non-essential position. Moreover it was recognized that since there are practical difficulties in accurately measuring insulin resistance, it was omitted as a component as other components such as waist circumference and triglycerides are so highly correlated with insulin resistance (18), that few of those with insulin resistance would be missed. The position and thresh-

Table 3. Ethnic specific cut points for waist circumference.

Ethnic group [†]	Waist circumference (as measure of central obesity)
Europids [§]	Male ≥ 94 cm Female ≥ 80 cm
South Asians	Male ≥ 90 cm Female ≥ 80 cm
Chinese	Male ≥ 90 cm Female ≥ 80 cm
Japanese	Male ≥ 85 cm Female ≥ 90 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available
Sub Saharan Africans	Use European data until more specific data are available
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available

[†] Ethnicity should be the basis for classification, not the country of residence.

In the USA the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes.

[§] In future epidemiological studies of populations of Europid origin, prevalence should be given using both European and North American cut points to allow better comparisons.

olds of other components were similar to those used in the ATPIII except for glucose, where the cut off of 5.6 mmol/l (100 mg/dl) recently recommended by the American Diabetes Association (24) was adopted for impaired fasting glucose.

The IDF Consensus group report has recommended further research on a comprehensive list of other components that should possibly be considered as additions in future definitions of the metabolic syndrome (19). The list includes: tomographic assessment of visceral adiposity and liver fat, adipose tissue biomarkers (adiponectin, leptin), apolipoprotein B, LDL particle size, formal measurement of insulin resistance and an oral glucose tolerance test, endothelial dysfunction, urinary albumin, inflammatory markers (C-reactive protein, tumour necrosis factor alpha, Interleukin 6 and thrombotic markers (plasminogen activator inhibitor factor-1, fibrinogen). These should be combined with CVD outcome assessment and development of diabetes so that in the future better predictors can be developed.

Of particular interest for Japan, is the possibility that

adiponectin might be included in future definitions of the syndrome because of the pioneering work of Matsuzawa and co-workers (26). Most adipokines are secreted at higher than normal levels in obesity and the metabolic syndrome, but adiponectin is an exception as its secretion is decreased in these disease states (24). It has been suggested that plasma levels of adiponectin may serve as a surrogate for insulin sensitivity (25). Further research findings on this are eagerly awaited.

In recent times, the metabolic syndrome has been the subject of vigorous debate. In a recent discussion paper, Kahn *et al.* (26) added to this dialogue with some very provocative statements. Kahn and colleagues questioned whether the condition can in fact be labelled a syndrome as the cause is unknown, and whether it serves any purpose other than labelling and medicalising people (26). Others have also suggested that the concept of the metabolic syndrome has been driven by the pharmaceutical industry to create new markets (27).

Despite these concerns, the IDF and the cardiovascular community are fairly adamant that the clustering of closely related risk factors for CVD and type 2 diabetes is sufficient evidence to call the condition a syndrome. Further, the identification of people who are high risk for CVD and diabetes, using the new IDF definition is very useful to clinicians and patients themselves. For those who are identified as having the syndrome, lifestyle change has been stressed as important first line treatment. Only when this fails, other options should be explored. This is not consistent with a syndrome claimed to be created by industry, which incidentally was first documented 80 years ago. Amid the burgeoning epidemics of type 2 diabetes and CVD worldwide, the need for identification and treatment of people with the syndrome is of paramount importance.

Nevertheless, it would be prudent to suggest that new IDF definition is the final chapter for the metabolic syndrome definition and further research may stimulate modification. It is hoped, however, that it will help identify those at increased risk, particularly those whom may not have been previously identified. It also may resolve some of the controversy surrounding this condition.

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