

Changing definitions of metabolic syndrome

Rakesh M. Parikh, Viswanathan Mohan¹

Department of Diabetology, S K Soni Hospital and D Clinic, Jaipur, ¹Dr Mohan's Diabetes Specialities Center, Chennai, India

ABSTRACT

The first description of patients with clustering of various metabolic abnormalities was as early as 1923 but it was more than five decades later, in 1988, that Reaven coined the term 'syndrome X' for this entity. The last two decades have brought forth a number of definitions and criteria to identify this condition. Various studies have demonstrated disparities in these definitions and a few researchers have questioned the utility of these criteria and even the existence of such a syndrome. A few important definitions are reviewed in this paper and, at the end, a simplified clinical definition is given and a simple parameter – lipid accumulation product – is described that can be used to identify this condition.

Key words: Controversies, definition, index of central obesity, metabolic syndrome

INTRODUCTION

A clustering of various metabolic abnormalities, e.g., hypertension, hyperglycemia, and hyperuricemia, was observed in some patients as early as 1923.^[1] More than five decades after this observation, Reaven coined the term 'syndrome X' for this conglomeration of various metabolic abnormalities, including glucose intolerance, hypertension, increased very-low-density lipoproteins (VLDL), triglycerides, and decreased high-density lipoprotein cholesterol (HDL-C), with insulin resistance being the basic underlying pathophysiologic problem.^[2] Over the last two decades, various organizations have proposed different definitions, using varying terminologies. We review a few important definitions in this paper.

WHO DEFINITION

WHO, in 1999, suggested a working definition of metabolic syndrome (MS), which was to be improved in due course of

time.^[3] WHO defined MS as glucose intolerance, impaired glucose tolerance (IGT) or diabetes mellitus (DM), and/or insulin resistance, together with two or more of the components listed below:

1. Raised arterial pressure, i.e., $\geq 140/90$ mm of Hg
2. Raised plasma triglyceride (≥ 150 mg/dl) and/or low HDL-C (<35 mg/dl in men and <39 mg/dl in women)
3. Central obesity, i.e., waist/hip ratio (WHR) >0.9 in men and >0.85 in women and/or body mass index (BMI) >30 kg/m²
4. Microalbuminuria, i.e., urinary albumin excretion rate ≥ 20 μ gm/minute or albumin/creatinine ratio ≥ 30 μ gm/mg.

This definition further insisted on a need for a clear description of the essential components of the syndrome, along with data to support the relative importance of each component. These conditions seem to be highly technical and the definition is rather impracticable.

EUROPEAN GROUP FOR STUDY OF INSULIN RESISTANCE DEFINITION

The European Group for Study of Insulin Resistance (EGIR) proposed a modification of the WHO definition, using the term *insulin resistance syndrome* rather than MS.^[4] According to the EGIR definition the diagnostic criteria included elevated plasma insulin ($>75^{\text{th}}$ percentile) plus two other factors from among the following:

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Corresponding Author: Dr Rakesh M. Parikh, B 09, Unnati Tower, Vidhyadhar Nagar, Jaipur 302 023, India. E-mail: drakeshparikh@gmail.com

1. Abdominal obesity: waist circumference (WC) ≥ 94 cm in men and ≥ 80 cm in women
2. Hypertension: $\geq 140/90$ mm of Hg or on antihypertensive treatment
3. Elevated triglycerides (≥ 150 mg/dl) and/or reduced HDL-C (< 39 mg/dl for both men and women)
4. Elevated plasma glucose: impaired fasting glucose (IFG) or IGT, but no diabetes

Notably, EGIR focused more on abdominal obesity than did WHO, but in contrast to WHO, EGIR excluded patients with type 2 DM from their syndrome because insulin resistance was viewed primarily as a risk factor for diabetes.

This definition was followed by a simpler definition released by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).^[5]

NCEP ATP III DEFINITION

According to this definition, a subject has the MS if he or she has three or more of the following criteria:

1. Abdominal obesity: WC ≥ 102 cm in men and ≥ 88 cm in women
2. Hypertriglyceridemia: ≥ 150 mg/dl (1.695 mmol/l)
3. Low HDL-C: < 40 mg/dl in men and < 50 mg/dl in women
4. High blood pressure (BP): $> 130/85$ mmHg
5. High fasting glucose: > 110 mg/dl

This definition differs from the WHO definition on several fronts. The NCEP ATP III did not believe that insulin resistance is mandatory for the development of MS and hence suggested the term MS instead of the previously used term 'insulin resistance syndrome.' This definition recognizes central obesity as the culprit and hence body mass index (BMI), which is a parameter for generalized obesity, has not been included in this definition. Central obesity has been quantified using WC instead of the WHR used by WHO. This definition considers low HDL and high triglycerides as separate components (both of them being individually atherogenic) rather than viewing dyslipidemia as a single component. The cutoff points used for BP and HDL are stringent as compared to those suggested in the WHO definition, but by avoiding the need for clamp techniques and measurement of microalbuminuria, the NCEP ATP III definition is much more practically applicable. The NCEP ATP III considers the proinflammatory state and prothrombotic state as components of MS though these have not been included among the criteria necessary to define MS.

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS DEFINITION

The American Association of Clinical Endocrinologists (AACE) too preferred using the term insulin resistance syndrome over MS.^[6] The major criteria they considered were IGT, elevated triglycerides, reduced HDL-C, elevated BP, and obesity. They did not specify any particular number of criteria for diagnosis, rather they left it to clinical judgment. They suggested that factors like family history of atherosclerotic cardiovascular disease or type 2 DM, polycystic ovary syndrome, and hyperuricemia be considered while exercising clinical judgement. Patients with type 2 DM were excluded from the definition of insulin resistance syndrome. The various components suggested by the AACE are as follows:

1. Some degree of glucose intolerance
 - IFG/IGT
2. Abnormal uric acid metabolism
 - Plasma uric acid concentration
 - Renal uric acid clearance
3. Dyslipidemia
 - Triglycerides
 - HDL-C
 - LDL particle diameter (small, dense LDL-particles)
 - Postprandial accumulation of TG-rich lipoproteins
4. Hemodynamic changes
 - Sympathetic nervous system activity
 - Renal sodium retention
 - Blood pressure ($\sim 50\%$ of patients with hypertension are insulin resistant)
5. Prothrombotic factors
 - Plasminogen activator inhibitor-1
 - Fibrinogen
6. Markers of inflammation
 - C-reactive protein, white blood cell count, etc.
7. Endothelial dysfunction
 - Mononuclear cell adhesion
 - Plasma concentration of cellular adhesion molecules
 - Plasma concentration of asymmetric dimethylarginine
 - Endothelial-dependent vasodilatation

ADA lowered the fasting plasma glucose threshold used to identify individuals with IFG from 110 mg/dl to 100 mg/dl. Subsequently, the NCEP ATP III has also suggested that the fasting plasma glucose concentration for diagnosing MS be lowered to 100 mg/dl.^[7]

Researchers worldwide preferred using the NCEP ATP III definition because it was relatively simple and clinically applicable. Various researchers noted that the WC cutoffs suggested by this definition were not applicable in other

countries.^[8-11] Though the WC cutoffs suggested by various groups differ, the generally accepted cutoffs for Asians are 90 cm for men and 80 cm for women.^[8,12]

INTERNATIONAL DIABETES FEDERATION GLOBAL CONSENSUS DEFINITION

Against the backdrop of all these controversies related to diagnostic criteria and the lack of consensus regarding WC cutoffs, the International Diabetes Federation (IDF) released a global consensus definition for MS, along with race- and gender-specific WC cutoffs.^[13] This definition identified central obesity as an essential component of MS and defined MS as central obesity (based on race- and gender-specific WC cutoffs) plus any two of the following four parameters:

- Raised triglycerides: ≥ 150 mg/dl (1.7 mmol/l) or history of specific treatment for this lipid abnormality
- Reduced HDL cholesterol: < 40 mg/dl (1.03 mmol/l) in males and < 50 mg/dl (1.29 mmol/l) in females or history of specific treatment for this lipid abnormality
- Raised blood pressure: systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg or on treatment for previously diagnosed hypertension
- Raised FPG: ≥ 100 mg/dl or previously diagnosed type 2 DM

The race- and gender-specific WC cutoffs suggested are as follows:

Country/Ethnic group	Waist circumference cutoff	
	Male	Female
Europeans In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes	≥ 94 cm	≥ 80 cm
South Asians Based on a Chinese, Malay, and Asian-Indian population	≥ 90 cm	≥ 80 cm
Chinese	≥ 90 cm	≥ 80 cm
Japanese	≥ 90 cm	≥ 80 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	

This global consensus definition was immediately followed by a joint statement from the American Diabetes Association and the European Association for the Study of Diabetes questioning the use of the term 'metabolic syndrome.' The statement concluded that too much critically important information is missing to warrant its designation as a 'syndrome.'^[14] It was also argued that having a label of MS does not add any risk in addition to the risk contributed by

the individual components.

This joint statement did not discourage researchers working in the field of MS and number of papers supporting the use of MS as screening tool to identify subjects at high risk of cardiovascular disease were published.^[15-18] Disparities in the data generated due to the use of various definitions still remained a major issue.^[19-23] For example, from the subanalysis of the Chennai Urban Rural Epidemiology Study, MS was identified in 546 subjects (23.2%) by the WHO definition, in 430 subjects (18.3%) by the NCEP ATP III definition, and in 607 subjects (25.8%) by the IDF definition. It is worthy of note that only 224 of these subjects were identified as MS by all the three criteria.^[6]

A joint interim statement of the IDF Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity suggested using the IDF global consensus definition, but without having central obesity as an obligatory parameter. It was suggested that the presence of three or more of the five parameters could be considered as diagnostic of MS.^[24] This joint statement suggested that the IDF-recommended race- and gender-specific cutoffs be used until WC cutoffs could be further evaluated based on data from various regions. The WC cutoffs suggested by various researchers from Japan,^[25,26] Korea,^[27,28] Iran,^[29] Iraq,^[30] and other regions^[31] has further confused the definition of MS as there are now numerous race- and gender-specific WC cutoffs.

Looking at the various race- and gender-specific cutoffs of WC suggested by the IDF and the corresponding average heights of the different population groups, it was postulated that the need for various race- and gender-specific cutoffs can be largely attributed to differences in the average heights (32). A novel parameter, the index of central obesity (ICO), defined as the ratio of the WC to the height, was suggested as an alternative.^[32] The utility of ICO for defining MS among diabetic^[33] as well as nondiabetic subjects^[34] has been evaluated.

The ICO has been widely studied and has been shown to have a good correlation with central adiposity^[35] and tissue glucose utilization;^[36] it was found to be a good predictor of type 2 DM.^[37] ICO has also been shown to have a strong correlation with leptin levels and atherogenic lipid profile,^[38] oxidative stress,^[39] and increased cardiovascular risk.^[40] Besides, it has been shown to be useful in identifying childhood central obesity^[41] and insulin resistance in children.^[42]

SIMPLIFIED DEFINITION OF METABOLIC SYNDROME

In view of all the above evidence, we have proposed that WC be replaced by ICO in all definitions of MS.^[43] With the use of ICO, the need for various race- and gender-specific cutoffs for WC can be obviated. Although a number of studies have proposed ICO cutoffs ranging between 0.45 and 0.55, we propose the use of a simple cutoff of 0.5 across both genders and all races. MS is a screening tool, and we believe that it should be used to identify people at high risk of metabolic complications and cardiovascular disease so that further detailed investigations can be performed. This definition translates into a very simple message to the community 'If your waist size is more than half of your height, you should consult your doctor.' Thus, all patients with ICO >0.5 should be evaluated for high blood pressure, prediabetes, and dyslipidemia.

INDIAN DIABETES RISK SCORE

Identification of MS can be made more clinical by including clinical parameters like age, family history, personal history, etc., as parameters to define MS. Indian diabetes risk score (IDRS) is one such parameter comprising simple clinical information like age, WC, family history of diabetes, and physical activity.^[44] IDRS \geq 60 been found to be useful in predicting MS and cardiovascular disease [Table 1].^[45]

LIPID ACCUMULATION PRODUCT

In view of the role of central obesity and dyslipidemia in atherosclerotic process, an alternative continuous index of lipid overaccumulation, the lipid accumulation product

(LAP), has been proposed. LAP is computed using WC and fasting triglycerides level (in mmol/l): $(WC - 65) \times TG$ (men) and $(WC - 58) \times TG$ (women).^[46] This parameter has been found to be better than BMI for predicting diabetes^[47] and has also been suggested for use in the identification MS.^[48] It has been shown to be a good predictor of cardiovascular disease^[49] though one study has shown that it may not be better than ICO or WHR for predicting cardiovascular disease.

CONCLUSION

In spite of the large number of controversies regarding the existence of MS as an entity and the nomenclature to be used, this conglomeration of various metabolic abnormalities has been widely accepted as a screening tool for identifying subjects at high risk of cardiovascular disease. While the various definitions proposed by different organizations have provided us with remarkable scientific insights into this syndrome, it has also complicated what was supposed to a simple screening tool. With the ongoing research in the area, we might soon have a very simple clinical definition to identify subjects at high risk of metabolic complications and cardiovascular disease.

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Parameter	Score
Age (years)	
<35	0
35-49	20
\geq 50	30
Abdominal obesity	
Waist <80 cm (female) , <90 (male) ^[45]	0
Waist \geq 80- 89 cm (female), \geq 90 - 99 cm (male)	10
Waist \geq 90 cm (female), \geq 100 cm (male)	20
Physical activity	
Exercise (regular) + strenuous work ^[45]	0
Exercise (regular) or strenuous work	20
No exercise and sedentary work	30
Family history	
No family history ^[45]	0
Either parent	10
Both parents	20
Minimum score	0

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