

A New International Diabetes Federation (IDF) Worldwide Definition of the Metabolic Syndrome: the Rationale and the Results

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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.¹ The metabolic syndrome now rears its head as one of the major public health issues of the 21st century. Associated with a 5-fold and 2-3 fold increase in type 2 diabetes cardiovascular disease (CVD),¹⁻³ it is thought to be a driver of the modern day epidemics of diabetes and cardiovascular disease and has become a major public health challenge around the world.¹ The premature morbidity and mortality resulting from cardiovascular disease and diabetes could cripple the health budgets of many nations, both developed and developing.

The metabolic syndrome is not a new condition as its description goes back at least 80 years being first described in the 1920s by Kylin, a Swedish physician, as the association of hypertension, hyperglycaemia, and gout.⁴ Marañón, the founder of modern Endocrinology in Spain explicitly described that "High blood pressure is a prediabetic state...that such a concept also applies to obesity...and that some constitutional predisposition underlies the association of diabetes (adult type), arterial hipertensión, obesity and perhaps also gout... also that diet is essential to prevent and treat those abnormalities."⁵ In 1947 in a classic paper, Vague drew attention to upper body adiposity (android or male-type obesity) as the obesity phenotype that was commonly

associated with metabolic abnormalities found in type 2 diabetes and CVD⁶ 20 years later, Avogaro, Crepaldi, and colleagues documented the simultaneous presence of obesity, hyperinsulinaemia, hypertriglyceridaemia, and hypertension.⁷ The clinical importance of the syndrome was highlighted another 20 years later by Reaven,⁸ who described the existence of a cluster of metabolic abnormalities, with insulin resistance as the central pathophysiological feature. He labelled it "syndrome X" but, surprisingly, Reaven did not include obesity, a factor that has been linked with the metabolic syndrome in all subsequent definitions.⁹⁻¹³

Since the first official definition of the metabolic syndrome by a WHO Working Group⁹ in 1999, a number of alternative definitions have been proposed. The most widely accepted of these have been produced by the European Group for the Study of Insulin Resistance (EGIR),¹⁰ and the National Cholesterol Education Program (NCEP) ATP III.¹¹

Pivotal to the WHO definition was the biological and physiological description of insulin resistance.⁹ Several limitations of the WHO definition were identified and the most important related to the use of the euglycaemic clamp to measure insulin sensitivity. This elaborate technology made the definition virtually impossible to use in both 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, 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 resistance¹⁰ (Table 1). The EGIR definition still retained insulin resistance as an essential component this was the major aetiological determinant of the metabolic syndrome. However, they 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 beta-cell dysfunction, a key characteristic of type 2 diabetes, makes estimates of

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insulin sensitivity unreliable. The EGIR definition also introduced waist circumference (94 cm for men and 80 cm for women) as the measure of adiposity.

Two years later, the NCEP introduced the ATPIII definition¹¹ (Table 1). Designed to have clinical utility, this definition did not include a specific measure of insulin sensitivity, and adopted a less “gluco-centric” approach by treating all components with equal importance. It had 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 very popular because of its simplicity. Its components are easily and routinely measured in most clinical and research settings. However, unlike the WHO definition, the ATPIII definition did not incorporate pro-inflammatory and pro-thrombotic variables as part of an extended definition.

To complicate matters further, the AACE developed a modification of the ATPIII definition. This was based on their belief that insulin resistance was the core feature.¹⁴ 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 risk factors. 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 AACE, by omitting abdominal

obesity as a key component, have evoked much criticism, because of the mounting evidence that it is a major risk factor for type 2 diabetes and cardiovascular disease.^{1,13}

These various definitions differed not only in the proposed components but also in the cut-off points used for each component, leading to considerable confusion. The confusion relates not only to the usefulness in the clinical setting but also was apparent in attempts to compare the burden of the metabolic syndrome in different populations. A detailed review on the prevalence of the syndrome using different criteria has been published recently.¹⁵ Notably, comparisons of published prevalences for different populations were difficult. There is an abundance of widely varying data comparing prevalences using different criteria and this only served to reinforce the need for a standardized definition internationally. As a result, the International Diabetes Federation (IDF) identified that there was an urgent need to rationalise the variety of definitions that had been developed for the metabolic syndrome. This need extended from clinical practice through to research.

As a result, the IDF asked its Epidemiology Task Force to gather experts from key regions around the globe to formulate a new, worldwide definition of metabolic syndrome. 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 Consensus group was chaired by two of us (GA and PZ) and the other members of the consensus group are listed below. The objective was to produce a new set of criteria for use both epidemiologically and in clinical practice worldwide in order to identify people

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 2 or more of the following	Plus 2 or more of the following	3 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 ≥1.7 mmol/L or HDL-C<0.9 (M) <1.0 (F)	2. Dyslipidaemia: triglycerides >2.0 mmol/L or HDL-C<1.0	2. Hypertriglyceridaemia: triglycerides ≥1.7 mmol/L
3. Hypertension: blood pressure ≥140/90 mm Hg or medication	3. Hypertension: blood pressure ≥140/90 mm Hg and/or medication	3. Low HDL-C: <1.0 mmol/L (M), <1.3 mmol/L (F)
4. Microalbuminuria: albumin excretion ≥20 µg/min	4. Fasting plasma glucose ≥6.1 mmol/l	4. Hypertension: blood pressure ≥130/85 mm Hg or medication
		5. Fasting plasma glucose ≥6.1 mmol/L

*WHO indicates World Health Organization; EGIR, European Group for the Study of Insulin Resistance; ATPIII, Adult Treatment Panel III; BMI, body mass index; WHR, waistship relation; HDL-C, high-density lipoprotein cholesterol; M, male; L, female
 †Defined as the top quartile of fasting insulin in the non-diabetic population.

with the metabolic syndrome, to better define the nature of the syndrome and to focus on lifestyle and therapeutic strategies to reduce the long term risk of both cardiovascular disease and type 2 diabetes.

A major component of this new initiative was to provide guidance on how to compensate for differences in waist circumference and in regional adipose tissue distribution between different populations, particularly Asians.^{1,16,17} The Consensus group also produced recommendations for additional criteria that could be included when studying the metabolic syndrome for research purposes. Finally, the IDF identified areas where more studies are currently needed, particularly research into the aetiology of the syndrome.

The IDF felt there was an urgent need for a single, universally accepted diagnostic tool that was simple to use in clinical practice and that did not rely upon measurements only available in research settings. This led to the IDF proposal of a new definition, which makes central obesity a necessary requirement (Table 2), and, for the first time, provides different obesity cut-off points for different ethnic groups.^{12,13}

The new IDF definition has taken into account the mounting evidence that central (abdominal) adiposity is common to each of the components of the metabolic syndrome.¹ An increased waist circumference, which is a well accepted proxy measurement for abdominal adiposity is now a necessary requirement for the diagnosis of the metabolic syndrome. This has the added advantage that simply measuring the waist serves as the first screening test for the syndrome and can be done easily, and cheaply, anywhere in the world. Ethnic-specific waist circumference cut-off points have been incorporated into the definition (Table 3) since research has shown that the levels of obesity at which the risk of other morbidities begins to rise varies between population groups.^{1,16,17} For example, for South and South-East Asians 90 cm and 80 cm are the cut-points for men and women respectively.¹³

Recognition of these metabolic syndrome features in people with impaired glucose metabolism and type 2 diabetes has special importance, as it indicates the need for aggressive cardiovascular risk reduction. As with many previous attempts to define diagnostic criteria for obesity, diabetes, hypertension, and dyslipidaemia, there is always a chance that new research will force changes including the possible incorporation of new components such as C-reactive protein, adiponectin and other adipokines.^{12,13} Fortunately, there are treatment regimens that can influence all of these risk factors. Most important, weight reduction and increased physical activity reduce insulin resistance improve glucose tolerance and other CVD risk factors, such as raised triglycerides and blood pressure.^{1,18,19} If these do not work then different pharmacological therapies are available to

deal specifically with each of the abnormalities i.e. raised blood pressure, raised triglycerides, low HDL-C and raised blood glucose. There are also newer drugs appearing which may either deal with 2 or more of the abnormalities or help with weight loss. In addition, smoking should be prohibited and alcohol consumption should be moderated.

Since the IDF released its new definition, there have been some very interesting, and indeed quite controversial, events! The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published an unprecedented joint report on the syndrome.²⁰ Based on a review of the earlier WHO⁹ and Adult Treatment Panel III¹¹ criteria, they raise several questions: 1) is it indeed a syndrome, particularly as the precise cause is unknown; 2) does it serve a useful purpose; and 3) is it labelling (and medicalising) people unnecessarily?

A major part of their stance is based on semantics. The IDF and the cardiovascular community are strongly united in the view that this clustering of closely related risk factors for CVD and type 2 diabetes is an excellent basis for calling this a syndrome. Many examples exist of conditions being given a name even when the precise underlying cause or causes, are unknown (e.g. type 2 diabetes). The IDF feels that it serves a useful purpose to focus on people, in both the community and clinical settings, who are at high risk of developing CVD and type 2 diabetes, particularly using the new IDF criteria proposed above.

The burgeoning epidemic of type 2 diabetes worldwide and CVD, particularly in the developing world seem adequate reasons for identifying and treating people with the syndrome. We believe that the new IDF criteria, which are now published in *The Lancet*¹³ are not the final word. Hopefully, they will help identify people at increased risk, and through further research will lead to more accurate predictive indices.

It is also very important to note that subsequent to the ADA/EASD criticisms, the American Heart Association and National Heart, Lung, and Blood Institute have just published a scientific statement on the metabolic syndrome²¹ that contains an updated ATP III classification (Table 4). In the updated ATP III classification, increased waist circumference is not deemed a necessity if 3 other risk factor criteria are present. The ATP III definition also allows for the lower waist circumference risk thresholds, particularly for Asian Americans. This updated ATP III version²¹ and the new IDF criteria¹³ identify essentially the same individuals as having the metabolic syndrome. Thus not only are ATP III and the IDF criteria virtually identical but so are their recommendations for clinical management.

In conclusion, the new IDF definition addresses both clinical and research needs. It also provides an

TABLE 2. IDF Metabolic Syndrome World-wide Definition

Central obesity <i>Waist circumference*—ethnicity specific</i>	
Plus any 2 of the following:	
Raised triglycerides:	≥1.7 mmol/L (150 mg/dL) or specific treatment for this lipid abnormality
Reduced HDL-cholesterol	<1.03 mmol/L (40 mg/dL) in males <1.29 mmol/L (50 mg/dL) in females or specific treatment for this lipid abnormality
Raised blood pressure	Systolic: ≥130 mm Hg or diastolic: ≥85 mm Hg or treatment of previously diagnosed hypertension
Raised plasma glucose†	Fasting plasma glucose ≥5.6 mmol/L (100 mg/dL) 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.

†In clinical practice, IGT is also acceptable, but all epidemiological 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.

accessible, diagnostic tool suitable for use in populations worldwide and establishes a list of potential additional criteria that should be included in epidemiological studies and other research into the metabolic syndrome.

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TABLE 3. Country/Ethnic Specific Values for Waist Circumference*

Country/Ethnic Group	Waist Circumference (as Measure of Central Obesity)
Europeans	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

*These are pragmatic cut points and better data are required to link them to risk. Ethnicity should be the basis for classification, not the country of residence.

TABLE 4. The American Heart Association and National Heart, Lung, and Blood Institute Updated ATP III Classification: 2005*

Any 3 of 5 criteria listed below constitute a diagnosis of metabolic syndrome

Categorical cut points:

- Elevated waist circumference†: 102 cm in men and 88 cm in women
- Elevated TG: 150 mg/dL (1.7 mmol/L) or drug treatment for elevated TG‡
- Reduced HDL-C: 40 mg/dL (0.9 mmol/L) in men, 50 mg/dL (1.1 mmol/L) in women, or drug treatment for reduced HDL-C‡
- Elevated BP: 130 mm Hg systolic BP or 85 mm Hg diastolic BP, or drug treatment for hypertension
- Elevated fasting glucose: 100 mg/dL or drug treatment for elevated glucose

*TG indicates triglycerides; BP, blood pressure.

†Some US adults of non-Asian origin (eg, white, black, Hispanic) with marginally increased waist circumference (eg, 94–102 cm [37–39 inches] in men and 80–88 cm [31–35 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cut point (eg, 90 cm [35 inches] in men and 80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

‡Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking 1 of these drugs are presumed to have high TG and low HDL.

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