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The IDF consensus worldwide definition of the metabolic syndrome

Part 1: Worldwide definition for use in clinical practice

Table 1: The new International Diabetes Federation (IDF) definition

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

Central obesity (defined as waist circumference \geq 94cm for European men and \geq 80cm for European women, with ethnicity specific values for other groups)

plus any two of the following four factors:

- **raised TG level:** \geq 150 mg/dL (1.7 mmol/L), or **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 **specific treatment for this lipid abnormality**
- **raised blood pressure:** systolic BP \geq 130 or diastolic BP \geq 85 mm Hg, or **treatment of previously diagnosed hypertension**
- **raised fasting plasma glucose (FPG)** \geq 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.

* These values have been updated from those originally presented to ensure consistency with ATP III cut-points

While the pathogenesis of the metabolic syndrome and each of its components is complex and not well understood, **central obesity** and **insulin resistance** are acknowledged as important causative factors.¹⁻⁵

Central (abdominal) obesity, easily assessed using waist circumference and independently associated with each of the other metabolic syndrome components including insulin resistance,^{2,6} is a prerequisite risk factor for the diagnosis of the syndrome in the new definition. Insulin resistance, which is difficult to measure in day-to-day clinical practice, is not an essential requirement.

Atherogenic dyslipidaemia describes the combination of raised triglycerides (TG) and low concentrations of HDL-c together with elevated apolipoprotein B (ApoB), small dense LDL and small HDL particles, all of which are independently atherogenic,⁷ and which is commonly observed in patients with both type 2 diabetes and the metabolic syndrome. Low HDL-c and high TG levels are frequently found with insulin resistance, with or without type 2 diabetes,⁸ and both are risk factors for coronary heart disease (CHD).^{9,10}



Table 2: Ethnic specific values for waist circumference

Central obesity is most easily measured by waist circumference using the guidelines in Table 2 which are gender and ethnic-group (not country of residence) specific. The consensus group acknowledges that these are pragmatic cut-points taken from various different data sources and that better data will be needed to link these to risk.

Country/Ethnic group		Waist circumference
Europids * <i>In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes</i>	Male	≥ 94 cm
	Female	≥ 80 cm
South Asians <i>Based on a Chinese, Malay and Asian-Indian population</i>	Male	≥ 90 cm
	Female	≥ 80 cm
Chinese	Male	≥ 90 cm
	Female	≥ 80 cm
Japanese**	Male	≥ 90 cm
	Female	≥ 80 cm
Ethnic South and Central Americans	<i>Use South Asian recommendations until more specific data are available</i>	
Sub-Saharan Africans	<i>Use European data until more specific data are available</i>	
Eastern Mediterranean and Middle East (Arab) populations	<i>Use European data until more specific data are available</i>	

* *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.*

** *Originally different values were proposed for Japanese people but new data support the use of the values shown above*

Although a higher cut-point is currently used for all ethnic groups in the USA for clinical diagnosis, it is strongly recommended that for epidemiological studies and, wherever possible, for case detection, ethnic group specific cut-points should be used for people of the same ethnic group wherever they are found. Thus the criteria recommended for Japan would also be used in expatriate Japanese communities, as would those for South Asian males and females regardless of place and country of residence.¹¹



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Part 2: 'Platinum standard' definition—additional metabolic criteria for research

The IDF consensus group has highlighted a number of other parameters that appear to be related to the metabolic syndrome (Table 3) which should be included in research studies to help determine the predictive power of these extra criteria for CVD and/or diabetes. The use of these additional factors in research will also allow further modification of the definition if necessary and the validation of the new clinical definition in different ethnic groups.

Table 3: Additional metabolic criteria for research

Abnormal body fat distribution	General body fat distribution (DEXA) Central fat distribution (CT/MRI) Adipose tissue biomarkers: leptin, adiponectin Liver fat content (MRS)
Atherogenic dyslipidaemia (beyond elevated triglyceride and low HDL)	ApoB (or non-HDL-c) Small LDL particles
Dysglycaemia	OGTT
Insulin resistance (other than elevated fasting glucose)	Fasting insulin/proinsulin levels HOMA-IR Insulin resistance by Bergman Minimal Model Elevated free fatty acids (fasting and during OGTT) M value from clamp
Vascular dysregulation (beyond elevated blood pressure)	Measurement of endothelial dysfunction Microalbuminuria
Proinflammatory state	Elevated high sensitivity C-reactive protein Elevated inflammatory cytokines (eg TNF-alpha, IL-6) Decrease in adiponectin plasma levels
Prothrombotic state	Fibrinolytic factors (PAI-1 etc) Clotting factors (fibrinogen etc)
Hormonal factors	Pituitary-adrenal axis



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Part 3: Recommendations for treatment

Once a diagnosis of the metabolic syndrome is made, the future management of the condition should be aggressive and uncompromising in its aim to reduce the risk of CVD and type 2 diabetes. Patients should undergo a full cardiovascular risk assessment (including smoking status) in conjunction with the following:

- **Primary intervention**

IDF recommends that primary management for the metabolic syndrome is healthy lifestyle promotion. This includes:

- moderate calorie restriction (to achieve a 5–10 per cent loss of body weight in the first year)
- moderate increase in physical activity
- change in dietary composition

The results of Finnish and American prevention of diabetes studies have shown the marked clinical benefits associated with a small weight loss in terms of preventing (or at least delaying by several years) the conversion to type 2 diabetes among high-risk individuals with glucose intolerance who were, generally, obese.^{12,13}

- **Secondary intervention**

In people for whom lifestyle change is not enough and who are considered to be at high risk for CVD, drug therapy may be required to treat the metabolic syndrome. While there is a definite need for a treatment that can modulate the underlying mechanisms of the metabolic syndrome as a whole and thereby reduce the impact of all the risk factors and the long term metabolic and cardiovascular consequences, these mechanisms are currently unknown and specific pharmacological agents are therefore not yet available. As defined in Table 4, it is currently necessary instead to treat the individual components of the syndrome in order that a reduction in the individual risk associated with each one will reduce the overall impact on CVD and diabetes risk.

Table 4: IDF recommended treatment of the individual components of the metabolic syndrome

Atherogenic dyslipidaemia
<p>Primary aims for therapy:</p> <ul style="list-style-type: none">• Lower TG (as well as lowering ApoB and non-HDL cholesterol)• Raise HDL-c levels• Reduce LDL-c levels (elevated levels represent a high risk in the metabolic syndrome) <p>Options:</p> <ul style="list-style-type: none">• Fibrates (PPAR alpha agonists) improve all components of atherogenic dyslipidaemia and appear to reduce the risk for CVD in people with metabolic syndrome. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) showed that raising HDL-c concentrations using a fibrate in patients with well-established CHD and both a low HDL-c and a low LDL-c level will significantly reduce the incidence of major coronary events.⁸• Statins to reduce all ApoB-containing lipoproteins and to achieve ATP III goals for



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LDL-c as well as for non-HDL-c (ATP III, 2001). Several clinical studies have confirmed the benefits of statin therapy.¹⁴⁻¹⁶

- Fibrates in combination with statins but may be complicated by side effects

Elevated blood pressure

- Categorical hypertension (BP $\geq 140/\geq 90$ mm Hg) should be treated according to the USA Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) recommendations.¹⁷
- In patients with established diabetes, antihypertensive therapy should be introduced at BP $\geq 130/\geq 80$ mm Hg.

Options:

- Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are useful antihypertensive drugs, with some clinical trials (but not all) suggesting they carry advantages over other drugs in patients with diabetes. At this time, however, the majority of clinical trials suggest that the risk reduction associated with antihypertensive drugs is the result of blood pressure lowering per se and not due to a particular type of drug.
- No particular agents have been identified as being preferable for hypertensive patients who also have the metabolic syndrome.

Insulin resistance and hyperglycaemia

There is growing interest in the possibility that drugs that reduce insulin resistance will delay the onset of type 2 diabetes and will reduce CVD risk when metabolic syndrome is present. The Diabetes Prevention Program (DPP) showed that metformin therapy in patients with prediabetes will prevent or delay the development of diabetes and recent thiazolidinedione studies have also demonstrated efficacy in delaying or preventing type 2 diabetes in patients with impaired glucose tolerance (IGT) and insulin resistance.^{18,19,20} Similarly, other studies have shown that both acarbose and orlistat can be used to delay the development of type 2 diabetes in patients with IGT.^{21,22}

Data do not yet exist to show whether any of the currently available thiazolidinediones reduce the risk of CVD in those with the metabolic syndrome, IGT or diabetes.

The group awaits with interest the results of ongoing thiazolidinedione and fibrate outcomes studies, as well as the publication of clinical data for the new generation of PPAR agonists which interact with both PPAR alpha and gamma receptors, thereby combining lipid and glycaemic effects. In addition, emerging therapies such as incretin mimetics, dipeptidyl peptidase IV inhibitors, protein tyrosine phosphatase 1B inhibitors, and the endocannabinoid receptor blocking agents offer potential as future therapies for the metabolic syndrome.



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Part 4: Future work

The IDF consensus group hopes that this new definition, emphasising the importance of central obesity with modifications according to ethnic group, will be adopted worldwide and prove convenient and useful in clinical practice and epidemiological studies. This should encourage the clinical diagnosis of the metabolic syndrome and the identification of patients at considerably increased risk of developing CVD and/or type 2 diabetes. A single worldwide definition will enable easier comparison of data from different studies and the ongoing refinement of the definition as more information becomes available and as the following areas of further research are explored:

- the aetiology of the metabolic syndrome
- the best and most predictive definition of the metabolic syndrome and its components
- how blood pressure is related to the other components of the syndrome
- the relationship between different constellations of factors to CVD outcomes
- the relationship of simple and complex measures of the components of the metabolic syndrome to clinical events
- the true impact of effective treatment of all components of the syndrome on CVD risk
- better identification of high risk patients with metabolic syndrome in different populations

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Metabolic syndrome—driving the CVD epidemic

Diabetes: a growing threat

Diabetes is one of the most common chronic diseases worldwide affecting nearly 200 million people (approximately 5 per cent of the adult population), and is the fourth or fifth leading cause of death in the developed world. If unchecked, by 2025 it is expected that diabetes will reach epidemic proportions, affecting 333 million people (a rise in prevalence to 6.3 per cent) globally. While much of this increase is expected to occur in developing countries, the reasons behind the increase are not country-specific but the consequence of population ageing, increasing urbanisation, unhealthy diets, obesity and sedentary lifestyles.¹⁻³

Diabetes and the metabolic syndrome—driving the CVD epidemic

Each year, 3.2 million people around the world die from complications associated with diabetes. In countries with a high diabetes incidence, such as those in the Pacific and the Middle East, as many as one in four deaths in adults aged between 35 and 64 years is due to the disease. Type 2 diabetes, which accounts for 90 per cent of all diabetes, has become one of the major causes of premature illness and death, mainly through the increased risk of cardiovascular disease (CVD) which is responsible for up to 80 per cent of these deaths.^{2,4}

These cardiovascular complications of diabetes, which is also a leading cause of blindness, amputation and kidney failure, account for much of the social and financial burden of the disease.^{2,3} The prediction that diabetes incidence will double by 2025 heralds a parallel rise in cardiovascular-related illness and death, with an inevitable and profound impact on global healthcare systems.

However, even before levels of blood glucose are high enough for a person to be diagnosed with diabetes, hyperglycaemia and related changes in blood lipids (increase in triglycerides and decrease in the 'good' cholesterol HDL-c) increase a person's risk of cardiovascular disease.²

The metabolic syndrome is a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure. It is estimated that around a quarter of the world's adult population have metabolic syndrome⁵ and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome.⁶ In addition, people with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes.⁷ The clustering of CVD risk factors that typifies the metabolic syndrome is now considered to be the driving force for a CVD epidemic.

Global burden

With a rise in comorbid disease on this scale, the burden on national healthcare systems and budgets is almost incalculable. It was estimated that in 2003 for the 25 European Union countries the total direct healthcare costs of all diabetes in 20 to 79 year olds was



approximately 64.9 billion international dollars (ID), equivalent to 7.2 per cent of the total health expenditure for these countries.^{2,8} The annual direct healthcare cost of diabetes worldwide for this age group is calculated to be as much as 286 billion, or even more. If diabetes prevalence continues to rise as anticipated, it is possible that this figure will increase to 396 billion. This will mean a spend of between up to 13 per cent of the world's healthcare budget on diabetes care in 2025, with high prevalence countries spending up to 40 per cent of their budget.²

It is important to note that these estimates of burden on national healthcare systems are for type 2 diabetes only and do not, as yet, estimate the additional burden of the cardiovascular disease associated with metabolic syndrome where clinical diabetes is not yet present.

What causes the metabolic syndrome?

In most people with glucose intolerance or type 2 diabetes, there is a multiple set of risk factors that commonly appear together, forming what is now known as the 'Metabolic Syndrome', but which has previously been termed 'Syndrome X',⁹ the 'Deadly Quartet'¹⁰ and more recently, the 'Insulin Resistance Syndrome'.^{11,12} This 'clustering' of metabolic abnormalities that occur in the same individual, and which appear to confer a substantial additional cardiovascular risk over and above the sum of the risk associated with each abnormality,^{6,13,14} has been the subject of intense debate with such groups as the WHO and the National Cholesterol Education Program – Third Adult Treatment Panel (NCEP ATP III) seeking to develop diagnosis and management guidelines around the combined presence of elevated blood sugar levels, an abnormal lipid profile, high blood pressure and abdominal obesity.^{15,16} If diabetes is not already present, the metabolic syndrome is a strong predictor for its development, the risk for type 2 diabetes being five times more likely in individuals with the syndrome.⁷

While each individual component of the metabolic syndrome confers an increased risk of cardiovascular-related death, this risk is more pronounced when the metabolic syndrome itself is present. The more components of the metabolic syndrome that are evident, the higher is the cardiovascular mortality rate.¹⁷

The underlying cause of the metabolic syndrome continues to challenge the experts but both insulin resistance and central obesity are considered significant factors.^{18,19} Genetics, physical inactivity, ageing, a proinflammatory state and hormonal changes may also have a causal effect, but the role of these may vary depending on ethnic group.^{20,21}

- **Insulin resistance**

Insulin resistance occurs when cells in the body (liver, skeletal muscle and adipose/fat tissue) become less sensitive and eventually resistant to insulin, the hormone which is produced by the pancreas to facilitate glucose absorption. Glucose can no longer be absorbed by the cells but remains in the blood, triggering the need for more and more insulin (hyperinsulinaemia) to be produced in an attempt to process the glucose. The production of ever-increasing amounts of insulin strains and may eventually wear out the beta cells in the pancreas, responsible for insulin production. Once the pancreas is no longer able to produce enough insulin then a person becomes hyperglycaemic (too much glucose in the blood) and will be diagnosed with type 2 diabetes. Even before this happens, damage is occurring to the body, including a build-up of triglycerides which further impairs insulin sensitivity and damage to the body's microvascular system (leading to kidney, eye and nerve damage).



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Strongly associated with irregularities in both glucose and lipid metabolism, insulin resistance is an underlying feature of the metabolic syndrome and type 2 diabetes.

- **Free fatty acids**

The mechanisms by which insulin resistance may exert an atherogenic effect include the build-up of **triglycerides (TG)** and **free fatty acids (FFA)**.

High concentrations of plasma FFA are common in type 2 diabetes, with early detection signifying a shift for the individual from impaired glucose tolerance (IGT) to type 2 diabetes. Insulin resistance in adipose tissue (fat cells) results in a flux of FFA from the adipose tissue to the liver causing insulin resistance in the liver and in peripheral tissues. Fatty acids block glucose oxidation and glucose transport, but they also cause **atherogenic dyslipidaemia** by inducing production in the liver of very low-density lipoprotein (LDL) particles that lead to the elevation of TG and apolipoprotein B (ApoB) and the lowering of high density lipoprotein cholesterol (HDL-c). An increase in TG, in addition to high LDL-c levels, significantly increases the risk for coronary heart disease (CHD),²² while low HDL-c is considered to be a particularly key risk factor for CVD in both non diabetic and diabetic individuals, as confirmed in epidemiological studies²³ and in the Lipid Research Clinics Prevalence Study²⁴ which found HDL-c to be an independent contributor to CVD in both men and women and a stronger risk factor for CVD in people with diabetes compared with non diabetic individuals. Significantly, low HDL-c and high TG are frequently found with insulin resistance, with or without type 2 diabetes.²⁵

This complex lipid profile, observed with both type 2 diabetes and the metabolic syndrome, is considered an extremely high risk factor for CVD as all of the abnormalities have been implicated as being independently atherogenic.^{22,26-29}

- **Central obesity**

Obesity, now thought to affect 50 to 60 per cent of a nation's population,² is associated with insulin resistance and the metabolic syndrome. Obesity contributes to hypertension, high serum cholesterol, low HDL-c and hyperglycaemia, and is independently associated with higher CVD risk.^{19,30,31} The risk of serious health consequences in the form of type 2 diabetes, CHD and a range of other conditions, including some forms of cancer, has been shown to rise with an increase in body mass index (BMI),³² but it is an excess of body fat in the abdomen, measured simply by waist circumference, that is more indicative of the metabolic syndrome profile than BMI.³³⁻³⁵ The International Obesity Task Force (IOTF) reports that 1.7 billion of the world's population is already at a heightened risk of weight-related, non-communicable diseases such as type 2 diabetes.³⁶

The mechanism by which excessive body fat causes insulin resistance and impairs glucose metabolism is not clearly defined but fat stores (particularly visceral adipose tissue) are an important cause of increased FFA and TG in the skeletal muscle, which impairs insulin secretion, raising blood glucose levels and the likelihood of developing diabetes. Excess adipose tissue (particularly the visceral fat tissue in the abdomen) also releases inflammatory cytokines that increase insulin resistance in the body's skeletal muscles. Furthermore, central obesity is also associated with a decreased production of adiponectin, which is the adipose-specific, collagen-like molecule found to have anti-diabetic, anti-atherosclerotic and anti-inflammatory functions.³⁷



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Eighty-five per cent of obese individuals have some degree of insulin resistance which can be improved with weight loss. Inactivity also plays a role via the mechanism of GLUT-4, a chemical which facilitates glucose absorption by the cells. Physical inactivity lowers levels of GLUT-4 making it less effective. Lack of exercise may also increase levels of FFA in the blood thus stepping up the storage of visceral fat, both of which are implicated in the aetiology of insulin resistance.

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Rationale for new IDF worldwide definition of metabolic syndrome

A clear need in clinical practice and in research

The International Diabetes Federation (IDF) gathered experts from around the world to formulate a new, worldwide definition of metabolic syndrome for the following reasons:

- IDF believes that metabolic syndrome is driving the twin global epidemics of type 2 diabetes and cardiovascular disease. The prevalence of metabolic syndrome is estimated to be around 20–25 per cent of the population.¹ People with metabolic syndrome are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome.² In addition, almost 200 million people globally have diabetes and 80 per cent of these will die from cardiovascular disease,³ so there is an overwhelming moral, medical and economic imperative to identify those individuals with metabolic syndrome early, so that lifestyle interventions and treatment may prevent the development of diabetes and/or cardiovascular disease.
- Existing guidelines put forward by the **World Health Organization (WHO)** and **National Cholesterol Education Program – Third Adult Treatment Panel (NCEP ATP III)**^{4,5} were never intended to provide exact diagnostic criteria for identifying individuals with metabolic syndrome in clinical practice.
- There is a stark need for a single, universally accepted diagnostic tool that is easy to use in clinical practice and that does not rely upon measurements only available in research settings.



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- The existence of multiple definitions for the metabolic syndrome has caused confusion and has resulted in many studies and research papers comparing the merits of each definition. It has also proved difficult to make direct comparisons between the data from studies where different definitions have been used to identify the syndrome.
- The new IDF definition addresses both clinical and research needs, providing an accessible, diagnostic tool suitable for worldwide use and establishing a comprehensive 'platinum standard' list of additional criteria that should be included in epidemiological studies and other research into the metabolic syndrome.

Existing 'definitions'

A number of expert groups have developed clinical criteria for the metabolic syndrome. The most widely accepted of these have been produced by the WHO, the European Group for the Study of Insulin Resistance (EGIR), and NCEP ATP III.⁴⁻⁶ All groups agree on the core components of the metabolic syndrome: obesity, insulin resistance, dyslipidaemia and hypertension. However, they apply the criteria differently to identify such a cluster.



The WHO and ATP III guidelines are summarised in Tables 1 and 2.

Table 1: WHO clinical criteria for the metabolic syndrome⁴

<p>In order to make a diagnosis of the metabolic syndrome a patient must present with glucose intolerance, impaired glucose tolerance (IGT) or diabetes and/or insulin resistance, together with two or more of the following components:</p> <ul style="list-style-type: none"> • Impaired glucose regulation or diabetes • Insulin resistance (under hyperinsulinaemic euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation) • Raised arterial pressure $\geq 140/90$ mm Hg • Raised plasma triglycerides (≥ 1.7 mmol/L; 150 mg/dL) and/or low HDL cholesterol (< 0.9 mmol/L, 35 mg/dL men; < 1.0 mmol/L, 39 mg/dL women) • Central obesity (males: waist to hip ratio > 0.90; females: waist to hip ratio > 0.85) and/or BMI > 30 kg/m² • Microalbuminuria (urinary albumin excretion rate ≥ 20g/min or albumin:creatinine ratio ≥ 30 mg/g)

Table 2: ATP III clinical identification of the metabolic syndrome⁵

Three or more of the following five risk factors:	
Risk factor	Defining level
Central obesity <ul style="list-style-type: none"> • Men • Women 	Waist circumference > 102 cm (> 40 in) > 88 cm (> 35 in)
Triglycerides	≥ 150 mg/dL (1.7 mmol/L)
HDL cholesterol <ul style="list-style-type: none"> • Men • Women 	< 40 mg/dL (1.03 mmol/L) < 50 mg/dL (1.29 mmol/L)
Blood pressure	$\geq 130/ \geq 85$ mm Hg
Fasting glucose	≥ 110 mg/dL (6.1 mmol/L)



The search for clarity

Because of the differences between the WHO and ATP III criteria, other groups such as the European Group for the Study of Insulin Resistance (EGIR) and the American Association of Clinical Endocrinology (AACE) have, at different times, documented modifications to the metabolic syndrome identification process.^{6,7} The **EGIR** version, preceding ATP III and designed to be used in non diabetics only, is simpler to use in epidemiological studies because it is dependent on fasting insulin levels to estimate insulin resistance and impaired fasting glucose (IFG) in place of IGT (avoiding the need for either a euglycaemic clamp or an oral glucose tolerance test (OGTT)). EGIR also proposed slightly modified measurements and cut-points for hypertension, triglycerides, HDL cholesterol and central obesity. The more recent **AACE** statement listed several identifying abnormalities including elevated triglycerides, blood pressure, fasting and post-load glucose (therefore requiring OGTT), in addition to a reduced HDL cholesterol and the presence of obesity and hypertension but stopped short of providing a specific definition of the syndrome, preferring instead that the diagnosis should rely on clinical judgment.⁷

The need for a global consensus

“Whichever definition is used and whatever the variation in the numbers due to the different criteria, when looking at prevalence data for the metabolic syndrome in different countries and across various ethnic groups, one fact is clear. Universally, the metabolic syndrome is a huge problem and is one that is growing at an alarming rate”.

Professor Sir George Alberti, co-author of the Consensus Statement

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