The IDF consensus worldwide definition of the

METABOLIC SYNDROME

International Diabetes Federation

IDF Communications
Avenue Emile De Mot 19,
B-1000 Brussels, Belgium
by fax at +32-2-5385114 or
by e-mail at communications@idf.org

The IDF worldwide definition of the metabolic syndrome was developed during a unique consensus workshop on the initiative of Professors Sir George Alberti and Paul Zimmet. The workshop was held on behalf of the IDF Task Force on Epidemiology and Prevention.

After the meeting, a writing group was convened including:

Sir George Alberti, London, UK
Paul Zimmet, Melbourne, Australia
Jonathan Shaw, Melbourne, Australia
Scott M. Grundy, Dallas, USA, *Consultant to Writing Group*

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Pablo Aschner - Bogotá, Columbia
Beverley Balkau - France
Philip Barter - Sydney, Australia
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John Brunzell - Seattle, USA
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Ralph DeFronzo - San Antonio, USA
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Markku Laakso - Kuopio, Finland
Pierre Lefèbvre - Liège, Belgium
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Jean Claude Mbanya - Yaounde, Cameroon
Chang Yu Pan - Beijing, China
Ambady Ramachandran - Chennai, India
Eberhard Standl - Munich, Germany
Michael Stern - San Antonio, USA
Jaakko Tuomilehto - Helsinki, Finland
Nigel Unwin - Geneva, Switzerland

Colette Kon, Rapporteur
IDF Executive Office: Anne Pierson

| The **metabolic syndrome**

The metabolic syndrome is a cluster of the most dangerous heart attack risk factors: diabetes and raised fasting plasma glucose, abdominal obesity, high cholesterol and high blood pressure.[1-4]

It is estimated that around 20-25 per cent of the world's adult population have the metabolic syndrome 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.

In addition, people with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes.[5] They would add to the 230 million people worldwide who already have diabetes[6a], one of the most common chronic diseases worldwide and the fourth or fifth leading cause of death in the developed world. The clustering of cardiovascular disease (CVD) risk factors that typifies the metabolic syndrome is now considered to be the driving force for a new CVD epidemic.

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 CVD which is responsible for up to 80 per cent of these deaths.[6b,7]

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'. This 'clustering' of metabolic abnormalities that occur in the same individual appear to confer a substantial additional cardiovascular risk over and above the sum of the risk associated with each abnormality.[8,9]

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 CVD.[8] The more components of the metabolic syndrome that are evident, the higher is the cardiovascular mortality rate.[10]

| **Global** burden

The 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.[11] The prediction that diabetes incidence will double by 2025 indicates a parallel rise in cardiovascular-related illness and death, with an inevitable and profound impact on global healthcare systems.

With a rise in comorbid disease on this scale, the burden on national healthcare systems and budgets is enormous. 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 up to 64.9 billion international dollars (ID), equivalent to 7.2 per cent of the total health expenditure for these countries.[6b,12]

The annual direct healthcare cost of diabetes worldwide for this age group is conservatively estimated to be as much as 286 billion ID, or even more. If diabetes prevalence continues to rise as anticipated, it is likely that this figure will increase to 396 billion ID by 2025. This will mean an expenditure of up to 13 per cent of the world's healthcare budget on diabetes care, with high prevalence countries spending up to 40 per cent of their budget.[6b]

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 CVD associated with metabolic syndrome where clinical diabetes is not yet present.

What causes the metabolic syndrome?

The underlying cause of the metabolic syndrome continues to challenge the experts but both insulin resistance and central obesity are considered significant factors.[13,14] 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.[15,16]

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 beta cells in 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 weakens and may eventually wear out the beta cells. 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.

Central obesity

Obesity 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.[13,17,18] The risk of serious health consequences in the form of type 2 diabetes, coronary heart disease (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),[19] 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.[20-22] 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.[23]

The need for early diagnosis and treatment: the IDF worldwide definition of metabolic syndrome

With the metabolic syndrome driving the twin global epidemics of type 2 diabetes and CVD 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.

A number of expert groups have developed clinical criteria for the metabolic syndrome. The most widely accepted of these were produced by the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), and the National Cholesterol Education Program – Third Adult Treatment Panel (NCEP ATP III).[24-26] All groups agreed on the core components of the metabolic syndrome: obesity, insulin resistance, dyslipidaemia and hypertension. However, the existing guidelines were either difficult to use or gave conflicting results when attempting to identify individuals with the metabolic syndrome in clinical practice.

Furthermore, 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.

IDF experts recognized that there was 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.

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.

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Worldwide definition for use in clinical practice

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.[15,16,27-29]

Central (abdominal) obesity, easily assessed using waist circumference and independently associated with each of the other metabolic syndrome components including insulin resistance, is a prerequisite risk factor

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* with ethnicity specific values)

plus any two of the following four factors:

Raised triglycerides	≥ 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 < 50 mg/dL (1.29 mmol/L) in females **or specific treatment for this lipid abnormality**
Raised blood pressure	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg **or treatment of previously diagnosed hypertension**
Raised fasting plasma glucose	(FPG) ≥ 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 >30kg/m², central obesity can be assumed and waist circumference does not need to be measured.*

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[30], and which is commonly observed in people 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[31], and both are risk factors for coronary heart disease (CHD).[32,33]

Table 2: Ethnic specific values for waist circumference

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

** 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.*

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.

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.[34]

'Platinum standard' definition– additional metabolic measurements for research

Table 3: Additional metabolic measurements 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

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.

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 a healthy lifestyle. 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 (as well as increased physical activity) 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.[35,36]

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. There is a definite need for a treatment that could 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. However, 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 lower individual risk associated with each component 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

Primary aims for therapy:

- 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)

Options:

- 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.[31]
- Statins to reduce all ApoB-containing lipoproteins and to achieve ATP III goals for LDL-c as well as for non-HDL-c (ATP III, 2001). Several clinical studies have confirmed the benefits of statin therapy.[37–39]
- Fibrates in combination with statins but may be complicated by side effects.

Elevated blood pressure

- Categorical hypertension (BP ≥ 140/≥ 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.[40]
- In patients with established diabetes, antihypertensive therapy should be introduced at BP ≥ 130/≥ 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 people 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 people 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 people with impaired glucose tolerance (IGT) and insulin resistance.[41-43] Similarly, other studies have shown that both acarbose and orlistat can be used to delay the development of type 2 diabetes in people with IGT.[44,45]

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.

| **Future** work

The IDF consensus group hopes that this new definition, emphasizing 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 an ongoing refinement 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
- the relationship of blood pressure 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.

Frequently Asked **Questions**

What is the objective of the new definition of the metabolic syndrome?

To provide a simple diagnostic and clinical tool to define those at greater risk of type 2 diabetes and CVD, detect them early and facilitate intervention. The tool will be particularly helpful in low-income countries where the metabolic syndrome is on an exponential rise. A single worldwide definition will also ease comparison of data from different studies.

Is the term "syndrome" adapted to the clustering of metabolic risk factors?

The term clearly fits the definition of a syndrome. For example, a well-accepted definition of a syndrome is a "group or recognizable pattern of symptoms or abnormalities that indicate a particular trait or disease".

What is the pathogenesis of the metabolic syndrome?

The primary underlying causes of the metabolic syndrome have been suggested to be central obesity and insulin resistance. However, more research is needed to establish whether there is one single factor or several which interact to give the characteristic picture of the metabolic syndrome. Environmental factors such as those associated with sedentary lifestyle may be important too.

Is the metabolic syndrome a valid indicator of cardiovascular risk?

The metabolic syndrome is not an *absolute risk predictor*. However, as a general rule, the risk from the metabolic syndrome for major CVD events is approximately twice as high as for those without the syndrome. The risk for type 2 diabetes is approximately five-fold. Finally,

people with type 2 diabetes who also present the metabolic syndrome carry a much higher risk of CVD than those who have type 2 diabetes alone.

Is the risk of CVD greater in the metabolic syndrome than the sum of its parts?

Some studies have shown a purely additive risk whilst others show a greater interaction. Whichever is true the metabolic syndrome provides a useful tool to identify high risk people and to institute treatment.

How can cardiovascular risk be prevented and treated?

Lifestyle change is the best way by far to prevent increased risk of cardiovascular disease and diabetes. If that fails then the individual risk factors will require treatment with appropriate pharmacological agents.

How can the metabolic syndrome be diagnosed in clinical practice?

The initial step is to measure waist circumference. This can be done by people themselves. If that is raised then the factors should be checked: blood pressure and a fasting blood sample for glucose, triglycerides and HDL-cholesterol.

In practice:

How is central obesity measured?

Central obesity is a prerequisite risk factor for metabolic syndrome which can be easily assessed using waist circumference. The waist measurement can be taken with a tape measure in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest. Ethnic specific values should be taken into account (see Table 2).

Have criteria been adapted to children and adolescents?

A further consensus meeting has been held by IDF on this subject and criteria to diagnose metabolic syndrome in children and adolescents will be published in late 2006 or 2007.

Have ATP III come in line with the new IDF criteria?

Apart from not making waist circumference the central and essential component, the most recent ATP III criteria are now in line with those of IDF.

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International Diabetes Federation

International Diabetes Federation (IDF)
Avenue Emile de Mot 19 • B-1000 Brussels • Belgium
Phone: +32-2-5385511 • Fax: +32-2-5385114
www.idf.org • communications@idf.org