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# Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation

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## Abstract

**Aims** To establish a unified working diagnostic tool for the metabolic syndrome (MetS) that is convenient to use in clinical practice and that can be used world-wide so that data from different countries can be compared. An additional aim was to highlight areas where more research into the MetS is needed.

**Participants** The International Diabetes Federation (IDF) convened a workshop held 12–14 May 2004 in London, UK. The 21 participants included experts in the fields of diabetes, public health, epidemiology, lipidology, genetics, metabolism, nutrition and cardiology. There were participants from each of the five continents as well as from the World Health Organization (WHO) and the National Cholesterol Education Program—Third Adult Treatment Panel (ATP III). The workshop was sponsored by an educational grant from AstraZeneca Pharmaceuticals.

**Consensus process** The consensus statement emerged following detailed discussions at the IDF workshop. After the workshop, a writing group produced a consensus statement which was reviewed and approved by all participants.

**Conclusions** The IDF has produced a new set of criteria for use both epidemiologically and in clinical practice world-wide with the aim of identifying people with the MetS to clarify the nature of the syndrome and to focus therapeutic strategies to reduce the long-term risk of cardiovascular disease. Guidance is included on how to compensate for differences in waist circumference and in regional adipose tissue distribution between different populations. The IDF has also produced recommendations for additional criteria that should be included when studying the MetS for research purposes. Finally, the IDF has identified areas where more studies are currently needed; these include research into the aetiology of the syndrome.

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**Keywords** central obesity, insulin resistance, International Diabetes Federation (IDF), metabolic syndrome, new definition

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**Abbreviations** AACE, American Association of Clinical Endocrinology; BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; CT, computed tomography; CVD, cardiovascular disease; EGIR, European Group for the Study of Insulin Resistance; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; IAF, intra-abdominal fat; IDF, International Diabetes Federation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL, low-density lipoprotein; MetS, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program—Third Adult Treatment Panel; OGTT, oral glucose tolerance test; PAI-1, plasminogen activator inhibitor-1; TG, triglycerides; TNF-α, tumour necrosis factor-alpha; WHO, World Health Organization; WHR, waist–hip ratio

## Introduction

The combination of metabolic disturbances now known as the metabolic syndrome (MetS) was first described by Kylin in the 1920s as the clustering of hypertension, hyperglycaemia and gout [1]. Two decades later, Vague noted that upper body adiposity (android or male-type obesity) was the type most often associated with the metabolic abnormalities seen with diabetes and cardiovascular disease (CVD) [2]. During the 1988 Banting Lecture, Reaven used the term 'Syndrome X' and firmly established the clinical importance of this syndrome, although obesity was not included [3]. In 1989, Kaplan renamed it 'The Deadly Quartet' and others then coined the term 'The Insulin Resistance Syndrome' [4,5]. It is now agreed that the well-established term 'metabolic syndrome' remains the most useful and widely accepted description of this cluster of metabolically related cardiovascular risk factors which also predict a high risk of developing diabetes (if not already present).

## Current definitions

A number of expert groups have attempted to develop a unifying definition for the MetS. The most widely accepted of these definitions have been 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) [6–8]. All groups agree on the core components of the MetS: obesity, insulin resistance, dyslipidaemia and hypertension. However, they provide different clinical criteria to identify such a cluster (see Table 1). For example, unlike the other two definitions, the ATP III definition does not obligatorily require impaired glucose regulation or insulin resistance as an essential component. In addition, the levels set for each component and the combination of components required to diagnose the MetS are slightly different in these three recommendations.

### WHO Definition (1999) [6]

The original WHO recommendations were not designed to be an exact definition, but were formulated as a working guideline to be improved upon in the future. The recommendations were part of a WHO report on the definition, diagnosis and classification of diabetes. The WHO definition is based on the assumption that insulin resistance is one of the major underlying contributors to the MetS. It therefore requires insulin resistance [or its likely surrogate, impaired glucose regulation, i.e. impaired glucose tolerance (IGT) or diabetes] to be present for the diagnosis to be made. In addition to insulin resistance, at least two other components must also be present (see Table 1) for the MetS to be diagnosed. The thresholds for systolic and diastolic blood pressures were changed between the provisional publication in 1998 and the definitive publication in 1999 [6,9].

The working criteria developed by the WHO have been criticised. The inclusion of microalbuminuria as a component is considered by some to be controversial. Moreover, the inclusion of a measurement of insulin resistance has also been open to criticism, since determining whether or not an individual is in the lowest quartile of insulin sensitivity (measured by clamp techniques) is virtually impossible in clinical practice or in epidemiological studies. Finally, the most appropriate measure of central obesity is also in dispute. Although the waist–hip ratio (WHR) may carry information relevant to disease endpoints, it is an index of the relative accumulation of abdominal fat. Waist circumference is a crude but relevant index of the absolute amount of abdominal fat and has been found to correlate better with visceral fat deposits as measured by computed tomography (CT) [10].

### EGIR Definition (1999) [7]

Following the publication of the WHO definition in 1999, the EGIR proposed a modified version to be used in non-diabetic subjects only, which is simpler to use in epidemiological studies since it does not require a euglycaemic clamp to measure insulin sensitivity (Table 1) [7]. EGIR proposed the use of fasting insulin levels to estimate insulin resistance and impaired fasting glucose (IFG) as a substitute for IGT. It also had slightly modified cut-points for hypertension, triglycerides (TGs), high-density lipoprotein (HDL) cholesterol and altered measures and cut-points for central obesity based on waist circumference.

 

**Table 1** Metabolic syndrome definitions

| | WHO (1999) [6] | EGIR (1999) [7] | NCEP ATP III (2001) [8] |
|---|---|---|---|
| | Glucose intolerance, IGT or diabetes and/or insulin resistance* together with two or more of the following: | Insulin resistance (defined as hyperinsulinaemia—top 25% of fasting insulin values among the non-diabetic population). Plus two of the following: | Three or more of the following five risk factors: |
| Fasting plasma glucose | | ≥ 6.1 mmol/l (110 mg/dl) but non-diabetic | ≥ 5.6 mmol/l (100 mg/dl)[a] |
| Blood pressure | ≥ 140/90 mmHg | ≥ 140/90 mmHg or treatment | ≥ 130/≥ 85 mmHg |
| Triglycerides | Raised plasma triglycerides: ≥ 1.7 mmol/l (150 mg/dl) *and/or* | > 2.0 mmol/l (178 mg/dl) or treatment *and/or* | ≥ 1.7 mmol/l (150 mg/dl) |
| HDL-cholesterol | Men: < 0.9 mmol/l (35 mg/dl) Women: < 1.0 mmol/l (39 mg/dl) | < 1.0 mmol/l (39 mg/dl) or treatment | Men: < 1.03 mmol/l (40 mg/dl) Women: < 1.29 mmol/l (50 mg/dl) |
| Obesity | Men: waist–hip ratio > 0.90 Women: waist–hip ratio > 0.85 and/or BMI > 30 kg/m$^2$ | Men: waist circumference ≥ 94 cm Women: waist circumference ≥ 80 cm | Men: waist circumference > 102 cm[b] Women: waist circumference > 88 cm |
| Microalbuminuria | Urinary albumin excretion rate ≥ 20 μg/min or albumin:creatinine ratio ≥ 30 mg/g | | |

*Insulin sensitivity measured under hyperinsulinaemic euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation.
[a]The 2001 definition identified fasting plasma glucose of ≥ 6.1 mmol/l (110 mg/dl) as elevated. This was modified in 2004 to be ≥ 5.6 mmol/l (100 mg/dl), in accordance with the American Diabetes Associations updated definition of impaired fasting glucose (IFG) [46,47,77].
[b]Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g. 94–102 cm (37–39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

**Table 2** American Association of Clinical Endocrinology (AACE) Position Statement on the insulin resistance syndrome* [11]

| | |
|---|---|
| 1. Triglycerides | 1.7 mmol/l (150 mg/dl) |
| 2. HDL-cholesterol | |
| Men | < 1.03 mmol/l (40 mg/dl) |
| Women | < 1.29 mmol/l (50 mg/dl) |
| 3. Blood pressure | > 130/85 mmHg |
| 4. Plasma glucose | |
| Fasting | 6.1–6.9 mmol/l (110–125 mg/dl) |
| 2-h post-glucose challenge | 7.8–11.1 mmol/l (140–200 mg/dl) |

*The diagnosis of the insulin resistance syndrome according to AACE is based on clinical judgement. Other factors to be considered in the diagnosis are overweight/obesity (body mass index ≥ 25 kg/m$^2$), a family history of Type 2 diabetes, polycystic ovary syndrome, sedentary lifestyle, advancing age and ethnic groups susceptible to Type 2 diabetes.

Further, if subjects were being treated for dyslipidaemia or hypertension they were considered to have the corresponding abnormalities.

### NCEP ATP III Definition (2001) [8]

The ATP III definition was presented in 2001 as part of an educational programme for the prevention of coronary heart disease (CHD). This definition was designed to facilitate diagnosis in clinical practice and differed in two major ways from the other definitions. First, it did not include a measure of insulin resistance as a component, and second, it was not 'glucose-centric', and treated glucose abnormalities as of equal importance with the other components in making the diagnosis. The ATP III guidelines state that the MetS may be diagnosed when a person has three or more of five components. These components are: central obesity, an elevated TG level, a reduced HDL-cholesterol level, elevated blood pressure and an elevated fasting glucose concentration (Table 1). Importantly, the ATP III definition includes waist circumference as the measure of obesity.

### The American Association of Clinical Endocrinology Position Statement (2002) [11]

More recently, the American Association of Clinical Endocrinology (AACE) has released a position statement on the 'insulin resistance syndrome' [11]. In this document, several factors are listed as identifying abnormalities of the syndrome. These include elevated TGs, reduced HDL-cholesterol, elevated blood pressure and elevated fasting and postload glucose (Table 2). Additional factors that increase the likelihood of the syndrome being present, such as obesity and hypertension, are also listed. The AACE statement deliberately does not provide a specific definition of the syndrome and allows the diagnosis to rely on clinical judgement.

 

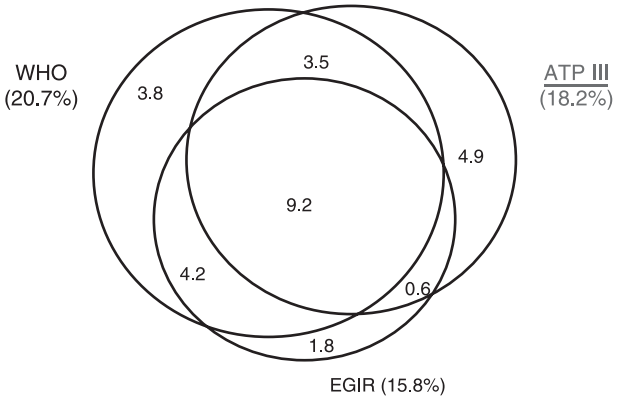


**Figure 1** Prevalence of the metabolic syndrome according to different definitions in an Australian non-diabetic population [12]. Data shown are percentage prevalences within the total population. All people with diabetes are excluded, as the European Group for the Study of Insulin Resistance definition specifically excludes diabetes.

**Table 3** Prevalence of components of the metabolic syndrome in men and women without diabetes in Europe [13]

| | Prevalence (%) | |
|---|---|---|
| | Men | Women |
| ≥ 2 of the components[a] | 35.3 | 29.9 |
| ≥ 3 of the components[a] | 12.4 | 10.7 |
| Hyperinsulinaemia plus any 2 or more of the other components[a] | 15.7 | 14.2 |
| Hyperinsulinaemia plus any 3 or more of the other components[a] | 7.7 | 6.3 |

[a]Components are: obesity, dyslipidaemia, impaired glucose regulation and hypertension.

## Clinical application of existing definitions

The differences in the prevalence of the MetS using WHO, EGIR and ATP III criteria can be demonstrated by data from the AusDiab study (a large national study of lifestyle and glucose intolerance) [12]. Although each definition identified approximately 15–21% of the Australian population as having the MetS, there was a large variability and only 9.2% of individuals met the criteria for all three definitions (Fig. 1). Similar results have been obtained in the DECODE study [13]. In non-diabetic subjects the overall prevalence of the MetS using modified WHO criteria was 15.7% in men and 14.2% in women. As expected, varying the number of components required to diagnose the MetS affected the prevalence of the syndrome (Table 3).

Importantly, the ATP III definition has a lower diagnostic threshold than the WHO definition for certain characteristics (i.e. HDL-cholesterol and hypertension) and a higher threshold for others (i.e. obesity). Therefore, although both the ATP III and WHO definitions identify approximately the same proportion of the population as having the MetS, the actual sets of people identified by the two criteria in the AusDiab study are not entirely congruent (Fig. 1). From the San Antonio Study it appears that the ATP III definition is superior to the WHO definition for predicting cardiovascular mortality [14]. In the same population, the ATP III definition was also superior for predicting diabetes [15], but the WHO definition was superior in Finnish men [16]. In terms of improving patient care, each definition needs to be able to predict hard clinical endpoints such as CVD. The current definitions are not as successful at predicting diabetes or CVD as are some of the established predicting models such as the Diabetes Predicting Model and the Framingham Risk Score [17].

**Table 4** Prevalence of the metabolic syndrome according to the World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR) and National Cholesterol Education Program—Third Adult Treatment Panel (NCEP ATP III)

| | WHO | EGIR | NCEP ATP III |
|---|---|---|---|
| Australia* | ≥ 30 years | > 24 years | > 24 years |
| Men | 25.2 | 18.6 | 19.5 |
| Women | 16.7 | 13.3 | 17.2 |
| France [78,79] | 30–64 years | 30–65 years | 30–64 years |
| Men | 23.0 | 16.4 | 10 |
| Women | 12.0 | 10 | 7 |
| Mauritius [80] | > 24 years | > 24 years | > 24 years |
| Men | 20.9 | 9.0 | 10.6 |
| Women | 17.6 | 10.2 | 14.7 |

*Unpublished data.

The existence of multiple definitions for the MetS has inevitably led to confusion and to the publication of many studies and research papers comparing the merits of each definition. Moreover, it is not possible to make direct comparisons between the data from studies when different definitions have been used to identify subjects with the syndrome. Just as the prevalence of the individual components of the syndrome varies between populations, so does the prevalence of the MetS itself. Differences in genetic background, diet, levels of physical activity, population age and sex all influence the prevalence of the MetS and its component parts [18]. The prevalence data for the MetS in different countries and different ethnic groups are summarized in Table 4 using the three main definitions. What is very clear from the epidemiological data is that the MetS is a frequent and increasing problem everywhere in the world.

## Rationale for a new world-wide definition

There is a strong need for one simple definition/diagnostic tool for clinical practice which could be used relatively easily in any country by any physician to identify patients at considerably increased risk of developing CVD and/or Type 2 diabetes. Such a definition would also allow comparison of the prevalence of the syndrome in different populations and its relationship with various health outcomes.

 

In May 2004 the IDF held an expert workshop to examine how the currently available definitions of the MetS could be improved and developed with the aim of reaching a consensus for the introduction of a new, unifying and working worldwide definition. The group considered it timely with the growing obesity epidemic to revisit and update levels and cut-points in the diagnosis of this syndrome. It was agreed that the definition should not only reflect the statistical clustering of the various potential components of the MetS, but also focus on the prediction of CVD. The consensus group intend that the definition should be easy to use in clinical practice and avoid the need for measurements usually only available in research settings. An additional aim of the workshop was to discuss treatment of those with the MetS and the prevention of diabetes and CVD.

The IDF workshop initially discussed the issue of whether the MetS is a syndrome in its own right. A syndrome is defined as a recognizable complex of symptoms and physical or biochemical findings for which a direct cause is not understood. With a syndrome, the components coexist more frequently than would be expected by chance alone [19]. When causal mechanisms are identified, the syndrome becomes a disease.

Statistical modelling approaches to the MetS have been used to provide insight into whether an underlying but unknown causal mechanism or mechanisms might explain its existence. Several problems emerge in attempting to understand better the nature of a syndrome when a cause is not apparent. Relying on statistical associations may lead to some components being included that may not be related to the underlying cause but instead may be related to one of the observed manifestations of the syndrome. Thus one could argue that this is the case for microalbuminuria, which is a component of the WHO definition of the MetS but not the ATP III definition. A number of statistical methods exist to make inferences about unobserved underlying factors involved in the MetS. Multiple factor analyses of the MetS have been conducted and these have not supported a unifying aetiological mechanism for this syndrome by consistently identifying one underlying factor. Other latent variable analytic techniques such as latent class analysis and confirmatory factor analysis have not been extensively applied in order better to define the MetS.

## General features of the MetS

Participants at the workshop agreed that the general features of the MetS include the following.

### Abnormal body fat distribution

Population studies have clearly shown that there is an increase in the risk of chronic non-communicable diseases associated with a progressive increase in total adiposity [as assessed by the body mass index (BMI)] [20]. Although epidemiological studies have shown that there is a greater prevalence and incidence of Type 2 diabetes, dyslipidaemia and CVD as a function of increasing BMI values, there is often remarkable heterogeneity amongst individuals with similar BMI values. It has been shown that among equally overweight or obese individuals, those characterized by an increase in abdominal fat (as assessed by waist circumference) are at increased risk of Type 2 diabetes and CVD [21,22]. This is independent of the risk predicted by increased BMI. CT assessment of visceral adiposity shows that those individuals with an excess of visceral adipose tissue are characterized by the most substantial adverse alterations in their metabolic risk profile [10]. Waist circumference provides a crude but effective measure of visceral fat but not necessarily in all subjects. Moreover, in the presence of an increased waist measurement, fasting hypertriglyceridaemia may represent a simple but useful marker of the possibility that the increased girth is due to visceral fat accumulation [23].

Although the use of waist circumference to assess abdominal adiposity is superior to BMI, the cut-off value for waist circumference is likely to be population specific as there are clear differences across ethnic populations in the relationship between overall adiposity, abdominal obesity and visceral fat accumulation [24–26]. Thus, although measuring the waist circumference is useful in every population of the world, waist cut-off values defining high-risk groups are likely to vary between populations. Studies to address this issue are clearly warranted.

### Insulin resistance

Insulin resistance is present in the majority of people with the MetS. It strongly associates with a number of other MetS components; however, the association with hypertension is weak. Insulin resistance correlates univariately with the risk of Type 2 diabetes and CVD. Although not all studies have shown it to be an independent CVD risk factor, a recent meta-analysis has shown a significant association in non-diabetic males and females between surrogate measures of insulin resistance and incident CVD [27]. The mechanisms underlying the link between insulin resistance and CVD still need further investigation.

### Atherogenic dyslipidaemia

The dyslipidaemia found in patients with the MetS presents in routine lipoprotein analysis as raised TGs and low concentrations of HDL-cholesterol. A more detailed analysis usually reveals other lipoprotein abnormalities, including elevated apolipoprotein B (Apo B), increased number of small dense low-density lipoprotein (LDL) particles and small HDL particles. All of these abnormalities are independently atherogenic [28].

### Elevated blood pressure

Elevated blood pressure associates with obesity and glucose intolerance and commonly occurs in insulin-resistant persons. The strength of the association varies considerably from one population to another.

 

#### Proinflammatory state

A proinflammatory state is recognized by elevated C-reactive protein (CRP) levels and is commonly present in people with the MetS [29]. A significant relationship was found between plasma CRP levels and measures of adiposity and of insulin resistance [30]. Data from the USA have shown that the risk of having an elevated CRP rises in a graded manner with increasing number of components of the MetS [31]. One contributory mechanism to this association is obesity, as adipocytes and macrophages release inflammatory cytokines which promote an inflammatory state [29].

#### Prothrombotic state

Components of the MetS are associated with both coagulation and fibrinolytic proteins, with a link to an elevated plasminogen activator inhibitor-1 (PAI-1) being the most consistent finding [32].

## The pathogenesis of MetS

While the pathogenesis of the MetS and each of its components is complex and not fully elucidated, two features appear to stand out as potential causative factors: insulin resistance and abnormal fat distribution (central obesity). Other factors have also been implicated in the development of the MetS, including genetic profile, physical inactivity, ageing, a proinflammatory state and hormonal dysregulation. It has been suggested that the role of these causal factors may vary depending on ethnic group [33,34].

#### Obesity

The IDF considers the obesity epidemic to be one of the main drivers of the high prevalence of the MetS. The prevalence of obesity is rising rapidly in many parts of the world [35–37]. Obesity contributes to hyperglycaemia, hypertension, high serum TGs, low HDL-cholesterol and insulin resistance, and is associated with higher CVD risk. Nonetheless, in the developed world, whilst BMI levels have been rising, CVD mortality has been falling or remaining static [38]. There is, however, a striking association of obesity with Type 2 diabetes [39,40].

The introduction of waist circumference in the EGIR definition rather than BMI has been a major conceptual advance, recognizing that it provides the most clinically useful indicator of central obesity and correlates well with insulin resistance.

With the development of imaging techniques to measure central fat precisely and to distinguish intra-abdominal (visceral) from subcutaneous fat, several studies have shown that central fat accumulation accompanied by an excess of omental adipose tissue is predictive of the features of the MetS [41, 42]. Furthermore, it has now been documented that individuals with a normal BMI may nevertheless be characterized by an excess of visceral adipose tissue and show the features of the MetS. A recent study has shown a strong and independent relationship between intra-abdominal fat (IAF) area and the MetS [41]. Interestingly, while IAF was independently associated with each of the ATP III MetS components, insulin sensitivity was independently related only to HDL-cholesterol, TGs and fasting glucose but not to blood pressure or central obesity.

Hypotheses relating central adiposity to the MetS focus on the newly emerging understanding that adipose tissue (particularly visceral adipose tissue) is a source of factors [including free fatty acids, tumour necrosis factor-alpha (TNF-α)] that impair insulin action in skeletal muscle. In addition, the adipose-specific collagen-like molecule, adiponectin, has been found to have antidiabetic, anti-atherosclerotic and anti-inflammatory functions [43]. Excessive adipose tissue is associated with a decreased production of adiponectin which may impair insulin sensitivity [44]. However, much work remains to be done to elucidate the complex interactions between central obesity and other MetS risk factors.

#### Insulin resistance

Evidence for a major role of insulin resistance in the development of the MetS is supported by the Bruneck Study, which examined the prevalence of insulin resistance in subjects aged 40–79 years using the homeostasis model assessment (HOMA) method [45]. In this study, the degree of insulin resistance correlated with the number of metabolic abnormalities and when several abnormalities were clustered together, insulin resistance was almost always present [46].

Insulin resistance is widely believed to be a central feature of the MetS, even though the mechanistic link between insulin resistance and most of the components of the MetS is not fully understood. Although insulin resistance is strongly associated with atherogenic dyslipidaemia and a proinflammatory state, it is less tightly associated with hypertension and the prothrombotic state. Finally, there are data to support the concept that insulin resistance or its associated hyperinsulinaemia are independent risk factors for CVD, but this association is yet to be confirmed in large-scale clinical trials [47].

The EGIR have recognized the need for a prospective evaluation of insulin resistance as an independent CVD risk factor and have designed the Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC) study. This study will examine insulin resistance and CVD risk in 1500 healthy people in 13 countries. Investigations will be repeated after 3 and 10 years to establish whether insulin resistance predicts deterioration of CVD risk markers, diabetes, obesity, atherosclerosis and CVD [48].

#### Other factors

Other important factors also influence the development of the MetS. For example, physical inactivity promotes the development of obesity and modifies muscle insulin sensitivity. Ageing is commonly accompanied by a loss of muscle mass and by an

 

increase in body fat, particularly in the abdomen; both of these changes can increase insulin resistance.

## Clinical outcome of MetS

The high prevalence of the MetS has important health implications.

### Cardiovascular disease

Since the metabolic syndrome comprises accepted CVD risk factors, it would be expected that the syndrome is a strong predictor of CVD. A substudy of the Botnia study, which involved over 4000 Finnish and Swedish adults, demonstrated that those with the MetS, as defined by the 1999 WHO criteria, were three times more likely to have a history of CHD compared with those without the syndrome. Furthermore, the presence of the syndrome was associated with a significant increase in cardiovascular mortality (12% vs. 2%) [49]. Other studies have confirmed that the risks of developing CVD, and of both cardiovascular and all-cause mortality, are increased by the presence of the MetS. Observational studies reporting these findings have included the European DECODE study [13], the Finnish Kuopio study [50], the San Antonio Heart Study [14] and the ARIC study [51]. Similar findings are also reported from clinical trials, including the WOSCOPS trial [52], and, at least for insulin resistance, the VA-HIT study [53].

Nonetheless, other studies have disputed whether the MetS gives any additional information over and above the individual well-known CVD risk factors [17]. This may relate to an inadequate definition of the MetS and the cutpoints used, rather than a problem with the overall concept.

### Diabetes

Non-diabetic people with the MetS are at a very high risk for the development of Type 2 diabetes. The risk for diabetes is up to fivefold higher in patients with the syndrome [17]. This is mainly due to the fact that glucose dysregulation is often already present (IFG or IGT). Importantly, the greatest impact of diabetes is the two to four times greater risk of CHD and stroke [54–56].

## New IDF metabolic syndrome world-wide definition and clinical criteria

The main aim of the IDF workshop was to produce a simple diagnostic tool for use in clinical practice and in research world-wide. This should facilitate a better understanding of the syndrome and targeting of care to people who would benefit from cardiovascular risk reduction. With this in mind, it was decided to use the 2001 ATP III definition as a starting point and to modify and update it to reflect the current objectives. Therefore, although it is recognized that insulin resistance is an important component of the MetS, its measurement is not essential to the new definition as it is difficult to measure in day-to-day clinical practice, whilst abdominal obesity is much easier to measure.

**Table 5** International Diabetes Federation metabolic syndrome world-wide definition

| | |
|---|---|
| Central obesity | Waist circumference*†—ethnicity specific (see Table 7) plus any two 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<br>< 1.29 mmol/l (50 mg/dl) in females<br>or specific treatment for this lipid abnormality |
| Raised blood pressure | Systolic: ≥ 130 mmHg<br>or<br>Diastolic: ≥ 85 mmHg<br>or treatment of previously diagnosed hypertension |
| Raised fasting plasma glucose‡ | Fasting plasma glucose ≥ 5.6 mmol/l (100 mg/dl) or previously diagnosed Type 2 diabetes<br>If > 5.6 mmol/l or 100 mg/dl, oral glucose tolerance test is strongly recommended but is not necessary to define presence of the syndrome |

*For guidelines on how to measure waist circumference accurately, see Table 7.
†If body mass index is > 30 kg/m$^2$ then central obesity can be assumed, and waist circumference does not need to be measured.
‡In clinical practice, impaired glucose tolerance 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-h glucose results can be added as supplementary findings.

The new definition is summarized in Table 5. According to the new definition, for a person to be defined as having the MetS, they must have central obesity plus any two of four additional factors. These four factors are:

- raised TG level: ≥ 1.7 mmol/l (150 mg/dl)
- reduced HDL-cholesterol: < 1.03 mmol/l (40 mg/dl) in males and < 1.29 mmol/l (50 mg/dl) in females (or specific treatment for these lipid abnormalities)
- raised blood pressure (systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg) (or treatment of previously diagnosed hypertension)
- raised fasting plasma glucose [FPG ≥ 5.6 mmol/l (100 mg/dl)] (or previously diagnosed type 2 diabetes).

### Central obesity

The new IDF definition differs from the ATP III definition in that it requires evidence of central obesity for the diagnosis of MetS. The rationale for this requirement is that central obesity is more strongly correlated with the other MetS features than is any other parameter [41] and is highly correlated with insulin resistance. Many reports support the view that central obesity/insulin resistance are constant features of the MetS.

Central obesity is most easily measured by waist circumference with cut-points that are gender and ethnic-group specific (Table 6). For example, an abnormal waist circumference for

 

**Table 6** Country/ethnic-specific values for waist circumference

| Country/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 | | Use European data until more specific data are available (Arab) populations |

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.
*In the USA the Adult Treatment Panel 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.
‡Based on a Chinese, Malay and Asian-Indian population.
§Subsequent data analyses suggest that that Asian values (male 90 cm; female 80 cm) should be used for Japanese populations until more data are available.

Europid males is ≥ 94 cm and for Europid females is ≥ 80 cm. These figures are based on cross-sectional data from Europids and were the best values for identifying people with increased adiposity, defined as a BMI of ≥ 25 kg/m$^2$ or WHR ≥ 0.90 for men and ≥ 0.85 for women [57]. Subsequently, these cut-points have been shown, in a random sample of 2183 men and 2698 women from the Netherlands, to be associated cross-sectionally with an adverse cardiovascular risk profile and have been adopted by WHO and EGIR [7,58,59].

The cut-points for central obesity adopted in the USA by the National Institutes of Health clinical guidelines for obesity were 102 cm for men and 88 cm for women [60]. These cut-points were employed by ATP III to define central obesity and correspond in Europid populations approximately to a BMI of 30 kg/m$^2$, or clinical obesity. However, ATP III recognized in the original document [8] that people with lower waist circumferences (e.g. 94–102 cm in men) can manifest characteristics of the MetS and, if so, should be treated similarly to those who have higher waist circumferences plus two other risk factors. Hence, the current IDF proposal does not represent a significant change from the ATP III obesity criteria.

Recommended cut-points for waist circumference vary for other ethnic groups. Cut-points for South Asians and Chinese are 90 cm and 80 cm for men and women, respectively. These cut-points have been recommended by the WHO [59] and

**Table 7** Guide to measuring waist circumference

Waist circumference should be measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest.
Australian data show that if body mass index is > 30, waist circumference is likely to be raised in the majority of people and measurement is not necessary.

values lower than those for Europids have been validated in a series of studies. Tan *et al*. showed that 89 cm for men and 79 cm for women were the best values in ROC analysis for predicting other MetS features in a Singapore population [25]. Similar analyses in other Chinese populations suggested cut-points of 80 cm in men and women [60,61] and 85 cm in men and 80 cm in women [62,63]. Data from Asian Indians showed that the risks of having diabetes increased significantly at a waist circumference of 85 cm in men and 80 cm in women [64]. Japanese data indicate cut-points of 85 cm in men and 90 cm in women based on correlations with visceral fat mass [65], although using these figures has produced odd results in relation to cardiovascular risk and prevalence. We are therefore now recommending the use of Asian values until more data have been obtained.

It is clear from these data that, for Asian populations, the risks of the MetS components rise at waist circumference values that are below the Europid cut-points. While the methods of calculating cut-points and the recommended cut-points have varied between studies, the current approach with ethnic group-specific cut-points is consistent with the WHO recommendations [59]. It is likely to provide a better assessment of obesity-related risk globally than have previous definitions with single cut-points. It is expected that future research will refine these cut-points.

It should be noted that the 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.

Waist circumference should be measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest (Table 7). Pragmatically, it is suggested that if BMI is greater than 30, then waist circumference does not need to be measured, as over 95% of these individuals will have a waist circumference above the gender- and ethnic-specific threshold values. This is based on analyses of population-based data from Australian Europids, and from Mauritius (predominantly Asian Indians) (J. Shaw, unpublished data).

### Dyslipidaemia

Dyslipidaemia is defined as either raised TG levels ≥ 1.7 mmol/l (150 mg/dl), low HDL-cholesterol < 0.9 mmol/l (40 mg/dl) for

 

men and < 1.29 mmol/l (50 mg/dl) in women, or specific treatment for previously detected hypertriglyceridaemia and/or reduced HDL-cholesterol. Modification of the HDL-cholesterol cut-point may be required in women in some populations [8].

#### Raised blood pressure

Raised blood pressure is defined as systolic pressure ≥ 130 mmHg, diastolic ≥ 85 mmHg, or antihypertensive treatment for previously diagnosed hypertension.

#### Hyperglycaemia

Hyperglycaemia is defined as IFG (as defined by the American Diabetes Association), IGT or diabetes. In clinical practice, the presence of any one of these glucose abnormalities will suffice. However, to ensure comparability between prevalence reports in epidemiological studies, the glucose criterion in such reports should always be based on the presence of either fasting hyperglycaemia (≥ 5.6 mmol/l or 100 mg/dl) or previously diagnosed diabetes. If fasting plasma glucose is 5.6–6.9 mmol/l (100–125 mg/dl) an oral glucose tolerance test (OGTT) is strongly recommended to identify IGT or undiagnosed diabetes, but is not necessary to define the presence of the MetS.

## Additional metabolic criteria

In addition to the new definition for the MetS, the IDF workshop participants have highlighted a number of other parameters that appear to be related to the MetS (Table 8). As many as possible of these additional measurements should be included in research studies. This would help determine the predictive power of these additional factors for CVD and/or diabetes. The use of these extra 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 8** Additional metabolic criteria for research

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

CT, Computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test; HOMA, homeostasis model assessment; TNF-α, tumour necrosis factor-alpha; PAI-1, plasminogen activator inhibitor-1.

## Recommendations for treatment

Once a diagnosis of the MetS is made, individuals should receive increased attention with the aim of reducing the risk for CVD and Type 2 diabetes. They should undergo a full cardiovascular risk assessment, which would include smoking status. Primary management for the MetS is healthy lifestyle promotion. This includes:

- moderate calorie restriction (to achieve a 5–10% loss of body weight in the first year)
- moderate increases in physical activity
- change dietary composition to reduce saturated fat and total intake, increase fibre and, if appropriate, reduce salt intake.

Whenever possible, a normal BMI and/or normal waist circumference ought to be a long-term target of lifestyle intervention. The results of the Finnish and American prevention of diabetes studies have, however, both 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, on average, obese [66,67]. Moreover, observational studies have shown that moderate to vigorous physical activity for 180 min per week reduces the risk of the MetS by 50%—with more vigorous exercise only 60 min is needed. In addition, an improvement in all lipid parameters has been observed with increased physical activity. Similar clinical trial data showing the impact of exercise on the development of CVD and diabetes are, however, lacking for people presenting with MetS.

In people who are considered to be at high risk for CVD, drug therapies may be required to treat the MetS. There is a definite need for a treatment that can modulate the underlying mechanisms of the MetS and thereby reduce the impact of all the risk factors and the long-term metabolic and cardiovascular consequences. As these mechanisms are currently unknown, specific pharmacological therapy is not yet available. It is therefore necessary to treat the individual components of the syndrome, including obesity, dyslipidaemia, abnormal glucose tolerance and elevated blood pressure.

 

#### Dyslipidaemia

Several drug alternatives may be considered in patients with atherogenic dyslipidaemia. Elevated LDL-cholesterol levels in patients with the MetS represent a high risk and are one of the primary targets of therapy. Other important therapeutic aims are to lower TG (as well as lowering Apo B and non-HDL-cholesterol) and to raise HDL-cholesterol. Statins will reduce all Apo B-containing lipoproteins and often can achieve the ATP III goals for LDL-cholesterol as well as for non-HDL-cholesterol (Table 9). Several clinical studies have confirmed the benefits of statin therapy. Fibrates improve all components of atherogenic dyslipidaemia and appear to reduce the risk for CVD. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) showed that raising HDL-cholesterol concentrations using a fibrate in patients with established CHD and both a low HDL-cholesterol and a low LDL-cholesterol level will significantly reduce the incidence of major coronary events [53]. The use of fibrates in combination with statins is particularly attractive, although it may be complicated by side-effects.

#### Elevated blood pressure

In patients with categorical hypertension (blood pressure ≥ 140/≥ 90 mmHg), drug therapies are required according to the USA Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommendations [68]. In patients with established diabetes, antihypertensive drugs should be introduced at an even lower blood pressure (≥ 130/≥ 80 mmHg). No particular antihypertensive agents have been identified as being preferable for hypertensive patients who also have the MetS.

Diuretics and β-blockers in high doses can worsen insulin resistance and atherogenic dyslipidaemia. For thiazide diuretics, doses should be kept relatively low in accordance with current recommendations. β-Blockers are cardioprotective in patients with CHD and are no longer contraindicated in patients with Type 2 diabetes. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are useful antihypertensive drugs and some clinical trials (but not all) suggest that they carry advantages over other drugs in patients with diabetes. At this time, however, the majority of clinical trials indicate that most of 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.

#### 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 the MetS is present. The Diabetes Prevention Program showed that metformin therapy in patients with IGT 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 IGT and insulin resistance [69–71]. 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 [72,73].

Further support for the concept of treating insulin resistance is apparent from the UKPDS, which showed that in Type 2 diabetes, treatment with metformin reduced CVD and mortality, whilst treatment with insulin or sulphonylureas did not show such an effect [74,75]. Data do not yet exist to show whether or not any of the currently available thiazolidinediones reduce the risk of CVD in those with the MetS, IGT or diabetes. One study has suggested that treating IGT patients with acarbose is associated with a significant reduction in the risk of CVD [76]. The results of various ongoing disease progression and cardiovascular outcome studies using several new drugs, such as thiazolidenediones, are awaited with interest.

The presence of the MetS in patients with Type 2 diabetes conveys particularly high risk for CVD. When both are present, appropriate treatment of dyslipidaemia and hypertension is essential in addition to the best possible glycaemic control. The choice of drug therapy, beyond lifestyle changes, to achieve the recommended glycaemic goal depends on clinical judgement.

## Future work

The participants at the IDF workshop hope that this new MetS definition emphasizing the importance of central obesity, with modifications according to ethnic group, will be adopted world-wide and prove convenient and useful in clinical practice and epidemiological studies. In this way, it should encourage the clinical diagnosis of the MetS and the identification of patients at considerably increased risk of developing CVD and/or Type 2 diabetes. Moreover, with a single world-wide definition it will be easier to compare data from different studies. Undoubtedly, the precise definition will continue to evolve as more information becomes available.

The group acknowledged that there are still many unanswered questions and areas where further research is needed. These include:

- the aetiology of the MetS
- the best and most predictive definition of the MetS and its components
- how blood pressure is related to the other components of the syndrome
- the relationship between different constellations of factors and CVD outcomes
- the relationship of simple and complex measures of the components of the MetS 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 MetS in different populations.

All participants agreed that lifestyle change is the best first-line treatment, but for many people with the MetS it will be not

 

**Table 9** Adult Treatment Panel III goals—comparison of low-density lipoprotein (LDL)-cholesterol and non-high-density lipoprotein (HDL)-cholesterol goals for three risk categories [8]

| | Risk category | |
|---|---|---|
| | LDL goal | Non-HDL goal |
| CHD and CHD risk equivalent (10-year risk for CHD > 20%) | < 2.6 mmol/l (100 mg/dl) | < 3.3 mmol/l (130 mg/dl) |
| Multiple (2 +) risk factors and 10-year risk ≤ 20% | < 3.3 mmol/l (130 mg/dl) | < 4.1 mmol/l (160 mg/dl) |
| 0–1 risk factor | < 4.1 mmol/l (160 mg/dl) | < 4.9 mmol/l (190 mg/dl) |

be enough. Polypharmacy will be an issue for subjects who are treated for a number of individual components of the MetS, and there is a significant need for new therapies targeting the MetS cluster as a whole.

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 peroxisome proliferator activated receptor (PPAR) agonists which interact with both PPAR-α and -γ 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 MetS.

Inevitably, there will be further modifications of the definition of the MetS in the future. We recommend strongly that future long-term studies should directed at: (i) defining the components of the MetS by measuring more precisely a wide range of variables, some of which are listed in Table 9, and in particular establishing the most predictive markers and cut-points for central obesity in different ethnic groups, and (ii) determining interventions which can prevent progression to CVD and Type 2 diabetes.

## Competing interests

K.G.M.M.A. receives periodic consultancy fees from Astrazeneca, GlaxoSmithKline, Novartis and Servier. P.Z. has received consultant fees from Novartis, GlaxoSmithKline, Bristol Myer Squibb, Bayer AG, Abbott and Merck and has received payment for speaking from E Merck, Sanofi-Aventis, Astra Zeneca, Kissei and Fournier. J.S. has received consultant fees from Merck, Eli Lilly and Novo Nordisk.

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