State of the Art

# Diagnosis of the Metabolic Syndrome: Which Definition Should We Use?

Evagelos N. Liberopoulos, Moses S. Elisaf

*Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece*

Key words:
**Metabolic syndrome, diagnosis, definition, diabetes, cardiovascular disease.**

*Manuscript received:*
April 5, 2005;
*Accepted:*
May 12, 2005.

*Address:*
Moses S. Elisaf

*Department of Internal Medicine,*
*School of Medicine,*
*University of Ioannina,*
*45110 Ioannina, Greece*
*e-mail:*
*egepi@cc.uoi.gr*

The metabolic syndrome (MetSyn) is a clustering of interrelated risk factors that identify individuals at increased risk for type 2 diabetes mellitus and cardiovascular disease.[1,2] Insulin resistance is believed to be the major underlying metabolic abnormality.[3] The incidence of the MetSyn increases with age, affecting more than 40% of those older than 60 years in the United States.[4] About a quarter of the adult population of the United States has the MetSyn, representing about 47 million Americans.[4] Data from the ATTICA[5] and the METS-GREECE[6] studies showed similar results in the Greek population.

As already stated, the presence of the MetSyn predicts a greater risk for events related to cardiovascular disease[7-10] and increased all-cause mortality.[11] The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[1,12] identified the components of the MetSyn that relate to cardiovascular disease (Table 1) and considered the "obesity epidemic" as mainly responsible for the rising prevalence of the MetSyn. Furthermore, Met Syn increases the risk of type 2 diabetes mellitus,[1,13] which in turn is a major risk factor for atherosclerotic disease. The MetSyn is also associated with a variety of other conditions (Table 2). The NCEP ATP III guidelines define the MetSyn as a new secondary target for cardiovascular disease risk reduction therapy beyond low-density lipoprotein cholesterol (LDL-C) lowering.[12] It follows that the diagnosis of the MetSyn is very important.[14] But how can we reach a diagnosis of the MetSyn?

At least 5 organisations have recommended clinical criteria for the diagnosis of the MetSyn.[12,15-18] These criteria are similar in many aspects, but they reveal fundamental differences concerning the predominant causes of the MetSyn and the definition of obesity.

In 1998, a World Health Organisation (WHO) group proposed a definition for the MetSyn (Table 3).[15] A potential disadvantage of the WHO criteria is the fact that, at least in some cases, special laboratory tests beyond routine assessment might be needed. In 1999, the European Group for the study of Insulin Resistance (EGIR) proposed its own criteria for the diagnosis of the MetSyn (Table 4).[16] The WHO and the EGIR definitions agree in that they both include either glucose intolerance or insulin resistance as an essential component.

The American Association of Clinical Endocrinologists proposed another set of criteria for the MetSyn (Table 5).[17] Obesity is not included in these criteria. A major disadvantage of this definition is that the number of risk factors needed for the diagnosis of the MetSyn is not specified, leaving the diagnosis to the health care provider's judgement.

The most applicable set of criteria in everyday clinical practice is that of the NCEP

**Table 1.** Features associated with the metabolic syndrome.[1,2,12,25]

- Abdominal obesity (↑ waist circumference)
- Atherogenic dyslipidaemia (↑ triglycerides, ↓ HDL-C, ↑ ApoB, ↑ small LDL particles)
- Elevated blood pressure
- Insulin resistance ± glucose intolerance (IFG and/or IGT)
- Proinflammatory state (↑ hsCRP)
- Prothrombotic state (↑ PAI-1, ↑ FIB)
- Other features: endothelial dysfunction, microalbuminuria, polycystic ovary syndrome, hypoandrogenism, non-alcoholic fatty liver disease, hyperuricaemia, and disturbances of the phosphate and magnesium metabolism

Apo – apolipoprotein, FIB – fibrinogen, HDL-C – high-density lipoprotein cholesterol, hsCRP – high-sensitivity C-reactive protein, IFG – impaired fasting glucose, IGT – impaired glucose intolerance, LDL – low-density lipoprotein, PAI – plasminogen activator inhibitor

**Table 2.** Clinical syndromes associated with the metabolic syndrome.[1,3]

1. Type 2 diabetes mellitus
2. Cardiovascular disease
3. Essential hypertension
4. Polycystic ovary syndrome
5. Non-alcoholic fatty liver disease
6. Certain forms of cancer
7. Sleep apnoea

ATP III (Table 6).[12] They include simple measurements that can be routinely performed by any health care provider. The criterion of insulin resistance or impaired glucose tolerance is not included in this definition. When 3 or more of the 5 listed criteria are present, a diagnosis of the MetSyn can be made. It should be noted that the presence of type 2 diabetes mellitus does not exclude a diagnosis of the MetSyn. The coexistence of type 2 diabetes mellitus and the MetSyn increases the risk of cardiovascular disease more than either condition alone.[9] However, these criteria and their cut points were rather arbitrary selected, since they were not based on the results of prospective studies but on the best opinion of an expert panel.

Abdominal obesity is more highly correlated with metabolic risk factors than elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the MetSyn.[19] In fact the MetSyn may be present even in normal-weight or slightly overweight individuals. In the United States' Third National Health and Nutrition Examination Survey, the prevalence of the MetSyn increased in a graded fashion from 0.9-3.0% at BMI 18.5-20.9 Kg/m$^2$ to 9.6-22.5% at BMI 25.0-26.9 Kg/m$^2$.[20] It should be noted that the defining level of waist circumference may be lower in populations at high-risk for the development of MetSyn (e.g. South Asians).

In 2003, the American Diabetes Association proposed that the fasting plasma glucose (FPG) level

**Table 3.** The World Health Organisation's clinical criteria for the metabolic syndrome.[15]

| **Insulin resistance, identified by one of the following:** |
|---|
| • Type 2 diabetes mellitus |
| • Impaired fasting glucose |
| • Impaired glucose tolerance |
| • Or for those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinaemic, euglycaemic conditions |
| **Plus any 2 of the following:** |
| • Antihypertensive medication and/or high blood pressure (≥140/90 mm Hg ) |
| • Plasma triglycerides ≥150 mg/dL |
| • HDL-C <35 mg/dL in men or <39 mg/dL in women |
| • Body mass index >30 kg/m$^2$ and/or waist to hip ratio >0.9 in men and >0.85 in women |
| • Urinary albumin excretion rate ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g |

HDL-C – high-density lipoprotein cholesterol

**Table 4.** The criteria of the European Group for the study of Insulin Resistance.[16]

| Insulin resistance-hyperinsulinaemia |
|---|
| • Top 25% of fasting insulin values from non-diabetic population |
| **Plus ≥2 of the following:** |
| • Antihypertensive medication and/or high blood pressure (≥140/90 mm Hg ) |
| • Dyslipidaemia: triglycerides ≥177 mg/dL or HDL-C <39 mg/dL |
| • Central obesity: waist circumference ≥94 cm (male) or ≥80 cm (female) |
| • Fasting glucose ≥110 mg/dL |

HDL-C – high-density lipoprotein cholesterol

**Table 5.** Clinical criteria of the American Association of Clinical Endocrinologists for diagnosis of the Insulin Resistance Syndrome.[17] Diagnosis depends on clinical judgement based on risk factors.

| Risk factor components | Cut points for abnormality |
|---|---|
| Overweight/obesity | Body mass index ≥25 kg/m$^2$ |
| Elevated triglycerides | ≥150 mg/dL |
| Low HDL-C | |
| Men | <40 mg/dL |
| Women | <50 mg/dL |
| Elevated blood pressure | ≥130/85 mm Hg |
| 2-hour post-glucose challenge | >140 mg/dL |
| Fasting glucose | 110-126 mg/dL |
| Other risk factors | • Family history of type 2 diabetes mellitus, hypertension, or cardiovascular disease<br>• Polycystic ovary syndrome<br>• Sedentary lifestyle<br>• Advancing age<br>• Ethnic groups having high risk for 2 diabetes mellitus or cardiovascular disease |

HDL-C – high-density lipoprotein cholesterol

used to identify individuals with impaired fasting glucose should be lowered from 110 to 100 mg/dL.[21] Subsequently, the NCEP ATP III has also suggested that the FPG concentration for diagnosing the MetSyn should be lowered to 100 mg/dL.[1]

Recently, the International Diabetes Federation (IDF) proposed a new definition of the MetSyn for use in clinical practice and epidemiological studies (Table 7).[18] This new definition has also already been adopted by the European Association for the Study of Diabetes and the European Atherosclerosis Society. Central obesity (as estimated by waist circumference) is a prerequisite risk factor for the diagnosis of the MetSyn in this new definition. Insulin resistance, which is difficult to assess in everyday clinical practice, is not an essential requirement. A diagnosis of the MetSyn can be made when central obesity plus 2 of the other 4 criteria (raised triglycerides, reduced high-density lipoprotein cholesterol [HDL-C], raised blood pressure and elevated FPG) are present. IDF waist circumference criteria are substantially lower than those of NCEP ATP III and they are gender and ethnic-group specific (Table 7). Moreover, the criterion for fasting glucose was set at 100 mg/dL. The criteria for triglycerides, HDL-C and blood pressure remained the same.

This new definition, if adopted worldwide, is expected to raise the prevalence of the MetSyn substantially. Athyros et al[22] showed that adoption of the new definition would increase the prevalence of the MetSyn by 77% ($p<0.0001$) compared with the NCEP ATP III criteria (43.4% vs. 24.5%, respectively) in subjects (n=9,669) representing the Greek population. Furthermore, the majority (up to 69%) of older age groups had IDF-defined MetSyn.[22] It is of interest that 2% of all subjects with NCEP ATP III MetSyn did not fulfil the obligatory abdominal obesity threshold of the IDF def-

**Table 6.** Clinical criteria of the national cholesterol education program adult treatment panel III for the diagnosis of the metabolic syndrome.[12] Three or more of the 5 criteria are required for the diagnosis.

| Criteria | Defining level |
|---|---|
| Abdominal obesity (waist circumference) | >102 cm in men<br>> 88 cm in women |
| Triglycerides | ≥150 mg/dL |
| HDL-C | <40 mg/dL in men<br><50 mg/dL in women |
| Blood pressure | ≥130/85 mm Hg |
| Fasting glucose | ≥110 mg/dL |

HDL-C – high-density lipoprotein cholesterol

**Table 7.** The International Diabetes Federation's definition of the metabolic syndrome.[18]

**Central obesity** (defined as waist circumference ≥94 cm for Europid men and ≥80 cm for Europid women, with ethnicity specific values for other groups*)

**Plus any 2 of the following 4 factors:**

- Raised triglyceride level ≥150 mg/dL, or specific treatment for this lipid abnormality
- Reduced HDL-C <40 mg/dL in males, <50 mg/dL in females, or specific treatment for this lipid abnormality
- Raised BP: systolic BP ≥130 or diastolic BP ≥85 mm Hg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose ≥100 mg/dL, or previously diagnosed type 2 diabetes

HDL-C – high-density lipoprotein cholesterol, BP – blood pressure

*South Asians and Chinese: ≥90 cm for males, ≥80 cm for females. Japanese: ≥85 cm for males, ≥90 cm for females. Ethnic South and Central Americans: Use South Asian recommendations until more specific data are available. East Mediterranean, Middle East (Arab) and sub-Saharan populations: Use European data until more specific data are available.

inition. On the other hand, subjects with only 1 or 2 NCEP ATP III diagnostic criteria often had MetSyn according to the IDF definition, as a result of the new lower limits for waist circumference and FPG.[22] Consequently, the IDF-MetSyn could then be considered a 'normal variant' if it is present in at least half of the population. Moreover, the IDF definition is also based on a consensus view and not on the findings of prospective clinical studies.

It is clear that a simple, practical and unified definition for the MetSyn is needed.[23,24] When several definitions are in use, it is difficult to compare prevalence and impact among different countries and different studies. We believe that the NCEP ATP III criteria are currently the most useful, at least in Caucasian populations. The new IDF definition takes into account ethnic differences but it seems to increase the incidence of the MetSyn unacceptably in the general population. Prospective studies to examine the ability of these 2 definitions to identify high-risk individuals should be carried out. The cost-effectiveness of treating subjects with the NCEP ATP III or IDF MetSyn should also be considered. The National Heart, Lung and Blood Institute and the American Heart Association are currently working to establish a unified definition for the MetSyn. Further consideration of the definition by the ATP III panel is expected to follow. Future research into additional components that are related to the MetSyn but are not currently included into its core definition (such as abnormal body fat distribution, atherogenic dyslipidaemia, endothelial dysfunction, proinflammatory and prothrombotic states or even disturbances of the phosphate and magnesium metabolism,[25] table 1) may allow further modification of the definition, if necessary.

### *Acknowledgement*

*Dr. Liberopoulos is partially funded by a grant from the Josef and Esther Gani Foundation (Ioannina, Greece).*

## References


1. Grundy S, Brewer B, Cleeman J, Smith S, Lenfant C: Definition of Metabolic Syndrome. Report of the National Heart, Lung and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004; 109: 433-438.
2. Gazi I, Liberopoulos E, Mikhailidis DP, Elisaf M: Metabolic syndrome: Clinical features leading to therapeutic strategies. Vasc Dis Prevent 2004; 1: 243-253.
3. Reaven GM: The Metabolic Syndrome: Requiescat in Pace. Clin Chem 2005; 51: 931-938.
4. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002; 287: 356-359.
5. Panagiotakos DB, Pitsavos C, Chrysohoou C, et al: Impact of lifestyle habits on the prevalence of the metabolic syndrome among Greek adults from the ATTICA study. Am Heart J 2004; 147: 106-112.
6. Athyros VG, Bouloukos VI, Pehlivanidis AN, et al: The prevalence of the metabolic syndrome in Greece: The MetS-Greece Study. Diabetes Obes Metab 2005; 7: 397-405.
7. McNeill AM, Rosamond WD, Girman CJ, et al: Prevalence of coronary heart disease and carotid arterial thickening in patients with the metabolic syndrome (The ARIC Study). Am J Cardiol 2004; 94: 1249-1254.
8. Girman CJ, Rhodes T, Mercuri M, et al: The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/ TexCAPS). Am J Cardiol 2004; 93: 136-141.
9. Athyros VG, Mikhailidis DP, Papageorgiou AA, et al: Prevalence of atherosclerotic vascular disease among subjects with the metabolic syndrome with or without diabetes mellitus: the METS-GREECE Multicentre Study. Curr Med Res Opin 2004; 20: 1691-1701.
10. Milionis HJ, Rizos E, Goudevenos J, Seferiadis K, Mikhailidis DP, Elisaf MS: Components of the metabolic syndrome and risk for first-ever acute ischemic nonembolic stroke in elderly subjects. Stroke 2005; 36: 1372-1376.
11. Lakka HM, Laaksonen DE, Lakka TA, et al: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002; 288: 2709-2716.
12. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-2497.
13. Liberopoulos EN, Tsouli S, Mikhailidis DP, Elisaf MS: Preventing type 2 diabetes in high risk patients: An overview of lifestyle and pharmacological measures. Curr Drug Targets 2005; in press.
14. Liberopoulos EN, Mikhailidis DP, Elisaf MS: Diagnosis and management of the metabolic syndrome in obesity. Obes Rev 2005; in press.
15. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabet Med 1998; 15: 539-553.
16. Balkau B, Charles MA: Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance. Diabet Med 1999; 16: 442-443.
17. Einhorn D, Reaven GM, Cobin RH, et al: American College of Endocrinology position statement on the insulin resistance syndrome. Endocr Pract 2003; 9: 237-252.
18. The IDF consensus worldwide definition of the metabolic syndrome: http://www.idf.org/webdata/docs/IDF-Metasyndrome_definition.pdf (accessed 14 June, 2005).
19. Grundy SM, Hansen B, Smith SC, Cleeman JI, Kahn RA: Clinical Management of Metabolic Syndrome. Report of the American Heart Association/National Heart, Lung and Blood Institute/American Diabetes Association Conference on Scientific Issues Related to Management. Circulation 2004; 109: 551-556.
20. St-Onge MP, Janssen I, Heymsfield SB: Metabolic syndrome in normal-weight Americans: new definition of the metabolically obese, normal-weight individual. Diabetes Care 2004; 27: 2222-2228.
21. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003; 26 (Suppl 1): S5-S20.
22. Athyros VG, Ganotakis ES, Elisaf M, Mikhailidis DP: The prevalence of the metabolic syndrome using the National Educational Program and International Diabetes Federation definitions. Curr Med Res Opin 2005; 21: in press.
23. Daskalopoulou SS, Mikhailidis DP, Elisaf M: Prevention and treatment of the metabolic syndrome. Angiology 2004; 55: 589-612.
24. Eckel RH, Grundy SM, Zimmet PZ: The metabolic syndrome. Lancet 2005; 365: 1415-1428.
25. Kalaitzidis R, Tsimihodimos V, Bairaktari E, Siamopoulos KC, Elisaf M: Disturbances of phosphate metabolism: another feature of the metabolic syndrome. Am J Kidney Dis 2005; 45: 851-858.