



## METABOLIC SYNDROME IN CLINICAL PRACTICE: CONSIDERATIONS ON DIAGNOSTIC CRITERIA AND PREVALENCE

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**Abstract.** The metabolic syndrome is defined as an association of risk factors of metabolic origin, combined with a heightened risk for cardiovascular diseases and for type 2 diabetes mellitus. The pathogenesis of the metabolic syndrome is multifactorial, the main risk factors being: obesity (abdominal obesity in particular) and insulin resistance. The prevalence of the metabolic syndrome is increasing in all countries, regardless of their developmental status. In non-diabetic patients, the prevalence of metabolic syndrome ranges between 15% to 30% and in subjects with type 2 diabetes mellitus, the prevalence is of 70%-90%. Prestigious medical associations have devised, over time, several models of diagnostic criteria, which differ both through the attention directed to the main risk factors and through the cut-off limits for the components. The existence of several definitions of the metabolic syndrome makes it difficult to compare the results of the large number of studies which have evaluated the presence of the metabolic syndrome and its association with the cardiovascular risk. Currently, there is an intense debate on the clinical utility of the metabolic syndrome diagnosis.

**Keywords:** metabolic syndrome, obesity, prevalence, cardiovascular risk

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### The evolution of the concept of metabolic syndrome

Although the concept of “metabolic syndrome” is a recent one, data on the association of cardiovascular risk factors dates back to 1923, when Kylin described a syndrome presenting hypertension, hyperglycemia and hyperuricemia. In 1947, Vague published an article on the relationship between the abdominal distribution of the fat tissue and various diseases, among which diabetes mellitus was mentioned [1]. The modern era of the metabolic syndrome began in 1967, when Avogaro and Crepaldi published a paper describing a syndrome comprised of dyslipidemia, hyperglycemia and obesity [2]. In 1977 the term “metabolic syndrome” was used by Haller for describing the association of obesity, diabetes mellitus, dyslipid-

emia, hypertension and hepatic steatosis [3] and by Singer for describing: obesity, hyperuricemia, diabetes mellitus, hypertension, dyslipidemia [4]. One of the milestones in the history of metabolic syndrome was the year 1988, when Reaven described the association of risk factors for diabetes and cardiovascular diseases, calling it „syndrome X”. Reaven introduced the concept of insulin resistance, showing that insulin resistance is present in most subjects with altered glucose tolerance and type 2 diabetes mellitus, as well as in approximately 25% of normal weight subjects, with normal glucose tolerance. Under these circumstances, the deterioration of glucose tolerance can be prevented only through increasing the insulin secretion of the beta pancreatic cells, thus perpetuating a state of chronic hyperinsulinemia [5]. In 1989 Keplan [6] renamed the syndrome as the “deadly quartet”, and in 1991-1992 Ferrannini and Haffner [7,8] proposed the new name of “insulin resistance syndrome”. In 1998, the World Health Organization (WHO) introduced the term “metabolic syndrome”.

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## Components of the metabolic syndrome.

### Diagnosis strategy

The following **metabolic risk factors** are associated within the metabolic syndrome [9,10]: *abdominal obesity*; *atherogenic dyslipidemia* (characterized both through an increase in the concentration of triglycerides, apolipoprotein B and of small dense LDL-cholesterol particles, and through a decrease in the concentration of HDL-cholesterol); *insulin resistance accompanied either by an increase of plas-matic glucose levels*; *an increase in blood pressure*; *prothrombotic state* (altering of the procoagulant factors – increased fibrinogen and factor VII; of the antifibrinolytic factors – increased concentration of the plasminogen activator inhibitor-1 (PAI-1); or altering of thrombocyte structure); *proinflam-matory state*.

Over time, several international organizations: WHO, EGIR (The European Group for the study of Insulin Resistance), NCEP-ATP III (The National Cholesterol Education Program – Third Adult Treatment Panel), AACE (American Association of Clinical Endocrinologists), IDF (International Diabetes Federation), AHA/NHLBI (American Heart Association and the National Heart, Lung and Blood Institute) have proposed different criteria for the diagnosis of metabolic syndrome. These criteria differ through the classification of the main risk factors. Thus, WHO, EGIR, AACE stress on insulin resistance, while NCEP-ATP III and IDF stress of abdominal obesity [1,9].

The first set of criteria for the diagnosis of meta-bolic syndrome was proposed in 1999 by WHO [11]. The WHO diagnosis required proof of insulin resistance, either through the existence of gluco-regulation issues (altered fasting plasma glucose, altered tolerance to glucose or type 2 diabetes mel-litus), either through the use of a hyperinsulinemic euglycemic clamp, which requires a level of glucose binding under the lowest quartile for the studied population. Together with insulin resistance, at least two of the following parameters need to be associ-ated: 1) arterial hypertension, BP  $\geq 140/90$  mmHg; 2) increased triglycerides concentration  $\geq 150$  mg/dl (1.7 mmol/l) and/or decreased concentration of HDL-cholesterol – men  $< 35$  mg/dl (0.9 mmol/l), women  $< 39$  mg/dl (1 mmol/l); 3) obesity – waist-to-hip ration: men  $> 0.9$ , women  $> 0.85$  and/or BMI  $> 30$  kg/m<sup>2</sup>; 4) microalbuminuria (urinary albumin excretion  $\geq 20$   $\mu$ g/min or albumin/creatinine  $\geq 30$  mg/g). In 1999, right after WHO published the diagnosis criteria, EGIR [1] proposed a modified version for non-diabetic subjects, keeping insulin re-sistance in the center of the diagnosis. EGIR defined insulin resistance as values of fasting insulinemia higher than the third quartile. In order to establish

a diagnosis of metabolic syndrome, together with insulin resistance, the association of at least two of the following parameters was required: 1) arterial hypertension, BP  $\geq 140/90$  mmHg or treatment; 2) increased triglycerides concentration  $> 177$  mg/dl (2 mmol/l) and/or decreased HDL-cholesterol  $< 39$  mg/dl (1 mmol/l); 3) central obesity–waist circumference: men  $\geq 94$  cm, women  $\geq 80$  cm; 4) fasting plasma glucose  $\geq 110$  mg/dl (6.1 mmol/l).

In 2001, in order to ease the clinical evaluation, the NCEP-ATP III criteria [12] were designed. For metabolic syndrome diagnosis, an association of at least three of the following five parameters is required: 1) central obesity–waist circumference: men  $> 102$  cm, women  $> 88$  cm; 2) increased tri-glycerides concentration  $\geq 150$  mg/dl (1.7 mmol/l); 3) decreased HDL-cholesterol – men  $< 40$  mg/dl (1.03 mmol), women  $< 50$  mg/dl (1.29 mmol/l); 4) arterial hypertension, BP  $\geq 130/85$  mmHg; 5) fasting plasma glucose  $\geq 110$  mg/dl (6.1 mmol/l). In 2005 AHA/NHLBI changed the NCEP definition through: decreasing the fasting plasma glucose levels to 100 mg/dl (according to the ADA definition - American Diabetes Association), including patients treated for hypertriglyceridemia, low HDL-cholesterol, arte-rial hypertension, clarifying the definition of high blood pressure (considering the criteria as fulfilled when either the systolic or the diastolic BP levels were heightened), including patients with waist circumferences of 102 cm in men and of 88 cm in women; for patients of Asian descent, lower cut-off values can be applied for the waist circumference (men  $\geq 90$  cm, women  $\geq 80$  cm).

In 2003, AACE changed the ATP III criteria, stressing on insulin resistance as main cause of the metabolic risk factors. Subjects with type 2 diabetes mellitus are excluded from the definition [13]. The major criteria employed are: altered glu-cose tolerance, increased triglycerides, decreased HDL-cholesterol, arterial hypertension, obesity. A minimum number of criteria are not required for diagnosis, leaving it up to the clinical evaluation of the patient.

In 2005, the IDF set forth a new definition of the metabolic syndrome [14]. The IDF diagnosis criteria, compared to those of the AHA/NHLBI, differed through three elements, as follows: ab-dominal obesity became a mandatory element for the diagnosis of metabolic syndrome, the cut-off values for the waist circumference were lowered and different cut-offs were introduced for differ-ent ethnical groups (for Europe: men  $\geq 94$  cm and women  $\geq 80$  cm). For diagnosing the metabolic syndrome at least two of the following parameters are needed: 1) increased plasma triglycerides con-centration  $\geq 150$  mg/dl (1.7 mmol/l) or specific treatment; 2) decreased HDL-cholesterol – men  $<$

40 mg/dl (1.03 mmol/l), women < 50 mg/dl (1.29 mmol/l) or specific treatment; 3) increased systolic blood pressure  $\geq$  130 mmHg or increased diastolic blood pressure  $\geq$  85 mmHg or specific treatment; 4) fasting plasma glucose  $\geq$  100 mg/dl (5.6 mmol/l) or type 2 diabetes mellitus formerly diagnosed.

### Epidemiologic concerns

The alarming increase in the prevalence of obesity leads to an increase in the prevalence of the metabolic syndrome. The results of epidemiologic studies show that a high percentage of the world population is affected by the metabolic syndrome. The prevalence of the metabolic syndrome increases with age and varies with sex and ethnicity.

The first centralized data on the prevalence of the metabolic syndrome have been generated through the analysis of the results obtained from 8,814 subjects over 20 years of age, which participated in the "Third National Health and Nutrition Examination Survey" (NHANES III) between 1988-1994. Using the ATP III definition, the prevalence of the metabolic syndrome was of 24%, similar in men and women. According to age, the prevalence of the metabolic syndrome increased to 6.7% in subjects aged between 20-29 years-old and to over 40% in those with ages over 60 years-old. Based on ethnicity, the prevalence of the metabolic syndrome was higher in subjects of Mexican origin (32%), women displaying a 26% higher prevalence, compared to men. Also, Afro-Americans registered a 56% higher prevalence in women compared to men [16].

In Europe, an analysis based on 8 studies which included a number of 8,200 men and 9,363 women showed that in non-diabetic individuals, with ages ranging from 40 to 55 years-old, the prevalence of the metabolic syndrome varied, according to the WHO definition, between 7% and 36% in men and between 5% and 22% in women [15]. Another analysis which included 6,156 men and 5,356 women, without diabetes, identified a prevalence of the metabolic syndrome in non-diabetic subjects of 15.7% in men and 14.2% in women [17].

There are wild differences between the results of prevalence studies for the metabolic syndrome, both because of the existence of several definitions of the metabolic syndrome, and due to the different characteristics of the studied populations. All the analyzed studies showed that maximal prevalence values for the metabolic syndrome are obtained when the IDF diagnostic criteria are used [18,19]. Welin [18], using three of the diagnosis definitions (NCEP/ATP-III, AHA/NHLBI and IDF), showed that the prevalence of the metabolic syndrome varied from 11% to 16% in women of around 50 years old, from 16% to 26% in men of the same age group and from 20% to 35% in men aged around 60

years old. The best rate of concordance is registered for the IDF and AHA/NHLBI diagnostic criteria, regardless of the characteristics of the studied population (diabetics or non-diabetics), the value of the concordance coefficient ranging between 0.8-0.85 [19,20]. The value of the concordance coefficient ranged between 0.6-0.68 [29] for the NCEP-ATP III and IDF criteria.

The prevalence of the metabolic syndrome in patients with type 2 diabetes mellitus varies between 70-90% [21,22,23]. Using the NCEP-ATP III diagnostic criteria, Alexander [21] showed that the **prevalence of the metabolic syndrome increases with the worsening of the glucoregulation issues**. Thus, the prevalence of the metabolic syndrome has increased from 26% in subjects with normal glucose tolerance to 33.1% in subjects with altered glucose tolerance, to 71.3% in subjects with altered basal glycemia, rising to 86% in subjects with type 2 diabetes mellitus.

### Discussions

There currently is a debate on the clinical utility of the metabolic syndrome diagnosis [24,25]. Several studies have shown that there is a connection between the metabolic syndrome and the cardiovascular risk [22,26,27,28]. The metabolic syndrome doubles the risk of developing a cardiovascular disease and increases 5-fold the risk for type 2 diabetes mellitus, results varying with the diagnosis criteria and with the characteristics of the analyzed populations.

Based on the fact that the metabolic syndrome is imprecisely defined, ADA-EASD (American Diabetes Association-European Association for the Study of Diabetes), make a common stand, questioning the ability of the metabolic syndrome to be an independent cardiovascular risk factor, and recommend approaching each traditional cardiovascular risk factor separately [25]. Wannamethe [29] showed that the Framingham risk score, compared to the metabolic syndrome, is a better predictor for the onset of coronary disease. Several other authors, Wang et al. [30], Mente et al. [31], Mottillo et al. [32] showed that although the metabolic syndrome is a risk factor for the onset of cardiovascular disease, the risk associated with the metabolic syndrome does not exceed the sum of the individual cardiovascular risk factors required for its diagnosis.

Abdominal obesity is at the center of metabolic syndrome's etiopathogenesis [33,34]. The connection between the visceral adipose tissue and the metabolic risk factors lies in the adipocyte secretion products, the adipokines. In obese subjects, most of the adipokines are excessively synthesized, having multiple proatherogenic roles, such

as: proinflammatory (TNF-alpha, IL-6, C-reactive protein), prothrombotic (PAI-1), chemoattractant for macrophages and monocytes (MCP-1) [35,36]. Special attention is focused on adiponectin, whose concentration decreases in obese subjects, being considered a unique hormone of the adipose tissue with antidiabetic, anti-inflammatory and antiatherogenic effects [37,38]. The connection with central obesity, particularly with its visceral distribution and insulin resistance, is explained through the following mechanisms: increased concentration of the nonesterified free fatty acids, result of a heightened lipolysis in the adipose tissue; deposits of triglycerides in the insulin-sensitive tissue (muscle and liver tissue); synthesis of adipokines, cytokines and hormones in the adipose tissue [33].

Based on the observation that there are subjects in whom an increase in the waist circumference is not associated with the other components of the metabolic syndrome, Lemieux [39] showed that the presence or absence of hypertriglyceridemia identifies the individuals at high cardiovascular risk, which associate an increase of the visceral adipose tissue, from the individuals at low cardiovascular risk, which associate an increase of the subcutaneous adipose tissue. Thus, through determining a series of simple variables, such as the waist circumference and the triglyceridemia ("hypertriglyceridemic waist"), using a value of  $\geq 90$  cm as cut-off for the waist circumference and  $\geq 177$  mg/dl (2 mmol/l) for triglycerides, we can identify the subjects which present the atherogenic metabolic triad (fasting hyperinsulinemia, increased concentration of apo B and small dense LDL-cholesterol particles).

In order to reconcile the two groups, for and against metabolic syndrome, the cardiometabolic risk model was developed; it includes the cardiovascular risk determined by traditional factors (LDL-cholesterol, HDL-cholesterol, hypertension, diabetes mellitus, age, male sex, smoking and genetic factors), associated with the cardiovascular risk determined by the presence of the metabolic syndrome [33].

## Conclusions

The prevalence of the metabolic syndrome is increasing, the highest prevalence being registered when the IDF diagnosis criteria are employed. The metabolic syndrome is associated with an increase in the risk for cardiovascular diseases and onset of type 2 diabetes mellitus. Yet, the simple presence of the metabolic syndrome does not indicate a heightened cardiovascular risk. A stratification of the cardiovascular risk in patients with metabolic syndrome requires both the precise diagnosis of abdominal visceral obesity and the expansion of the diagnosis components through including other

criteria associated to the metabolic syndrome, as for example the inflammatory markers (C-reactive protein), adipocytes' secretion products (adiponectin), atherogenic dyslipidemia marker (apo B). A first step in treating patients with metabolic syndrome, is addressing the cardiometabolic risk factors through lifestyle change, losing weight and exercising. Consequently, each risk factor shall be treated independently, according to the current guidelines.

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