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METABOLIC SYNDROME – THE "SILENT KILLER", A CONTINUING CHALLENGE

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Abstract

Metabolic syndrome, also known as dysmetabolic/plurimetabolic syndrome, X syndrome, insulinresistance syndrome or deadly quartet is an aggregate of interrelated metabolic abnormalities that occur with a higher prevalence in people with insulinresistance or with compensatory hyperinsulinism and identifies subjects who are at risk for developing type 2 diabetes and cardiovascular disease. In addition, individuals with metabolic syndrome are at increased risk of developing polycystic ovarian syndrome, non-alcoholic fatty liver, gallstones (cholesterol stones), sleep apnea, asthma and some forms of cancer.

key words*: metabolic syndrome, insulinresistance, hyperinsulinism, type 2 diabetes*

Introduction

Metabolic syndrome is a clinical construction useful in preventive medicine with reference to metabolic and cardiovascular diseases, oncology and hepatology.

Metabolic syndrome (MS), clinical entity recently individualized, a clinical concept with multiple definitions expresses a complex disorder of the body's energy metabolism which has insulin resistance and hyperinsulinism as central element [2] associated with the presence of risk factors involved in the etiology and/or pathophysiology of atherosclerosis.

In 1998, Reaven was the first who interpret the association between diabetes, obesity, dyslipidemia and arterial hypertension by their pathogenic relationship with peripheral insulin resistance [3]. He demonstrated that insulin resistance and compensatory hyperinsulinism predispose patients to dyslipidemia, type 2 diabetes and arterial hypertension and thus causes many cases of cardiovascular disease.

In the effort to introduce the treatment of metabolic syndrome in clinical medical practice, several organizations have attempted to develop a definition and a set of criteria to facilitate diagnosis of this disease.

The first proposal came in 1998 when **WHO** said that the main sign of this disease is insulin resistance. Besides this main criterion for the diagnosis of metabolic syndrome, the patient is required to submit other two factors: obesity, hypertension, elevated triglycerides,

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low HDL or microalbuminuria, increased blood sugar.

In 1999 the **European Group for the Study of Insulinresistance (EGIR)** proposed to amend the definition of WHO. It recognizes that insulin resistance is a major factor in metabolic syndrome, but EGIR give more importance to abdominal obesity and exclude the fact that patients with diabetes are more predisposed to develop metabolic syndrome.

2001 comes with a new proposal for defining metabolic syndrome, made by **National Education Program - Adult Treatment Panel III**. Alternative clinical criteria were introduced for defining metabolic syndrome, the diagnosis depends not specifically on the existence of insulin resistance, but the presence of 3 of 5 criteria: abdominal obesity, elevated triglycerides, low HDL-C, hypertension, increased fasting glucose. In 2001 [4], **National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATP III)** [2] has developed another definition, reiterated in 2005 when it was discussed with experts AHA [5] that metabolic syndrome is a "multiplex" cardiovascular risk factor which includes six components: insulin resistance with or without glucose intolerance, abdominal obesity, atherogenic dyslipidemia, hypertension, prothrombotic and proinflammatory status. This combination of factors determine the presence of cardiovascular risk higher than traditional isolated factors: hypertension, hypercholesterolemia, smoking, diabetes mellitus [1].

NCEP-ATP III experts state that apart from cardiovascular diseases and diabetes, people with metabolic syndrome are liable for the occurrence of other conditions or diseases such as polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disorders and certain forms of cancer (breast and prostate).

American College of Endocrinology definition actually refers to the insulin resistance syndrome characterized by four factors: increased triglycerides, decreased HDL cholesterol, hypertension and glucose tolerance [6]. Surprisingly, the definition of obesity is missing.

IDF Guide, launched in 2005, says that metabolic syndrome is a clustering of metabolic abnormalities associated with increased cardiovascular risk and diabetes. The central element is the definition of abdominal obesity, plus prediabetes or diabetes, hypertriglyceridemia, low HDL cholesterol and hypertension [7].

2009 is the year that was given the last definition. The latest agreement was published in october 2009, representing the viewpoint of the **International Diabetes Federation (IDF), National Heart, Lung, Blood Institute (NHLBI), American Heart Association (AHA), the World Heart Federation, International Atherosclerosis Society and International Association for the Study of Obesity (IASO)** which establishes that the metabolic syndrome [2] is a complex of risk factors for cardiovascular disease and diabetes. These interrelated factors are:

- Disglycaemia
- Increased blood pressure
- High levels of triglycerides
- decrease in HDL cholesterol
- Obesity (especially abdominal)

At these factors are added prothrombotic and proinflammatory state. Insulin resistance may be the common pathogenetic element, although there are still many controversies on

the subject [2]. The syndrome, as a concept, is defined as a simple combination of factors, which occurs frequently, but without a specified cause.

This definition should not be confused with diagnostic criteria. If hyperglycemia is present shall be interpreted within the concept of dysglicemia. This includes any value associated with increased cardiovascular risk in blood glucose, basal blood glucose (basal glucose ≥100mg/dl and ≤125mg/dl), decreased glucose tolerance (blood glucose at 2 hours post-load in TTOG ≥140mg/dl and ≤199mg/dl), diabetes mellitus.

Table 1. Diagnosis of MS elements, partially rival [8]

	WHO 1998	AHA	ADA 2001	ATP III 2001	IDF 2005/2009
Insulin Resistence	+	+	+	+	+
Low HDL	+	+	+	+	+
Artherial hypertension	+	+	+	+	+
HighTG	+	+	+	+	+
Central obesity	+	+	+	+	+
Impaired glucose tolerance	+	+	+	+	+
Diabetes	+	+	-	-	+
High LDL	-	-	-	-	-

A very useful conceptual reconciliation is published by S.M. Grundy [9] to establish the link between cardiologists and diabetologists. The same author dominates a round table of which conclusions likely announced the harmonized consensus of 2009 [10]. Attempt to harmonize the metabolic syndrome was followed almost immediately by the publication of the WHO report which recognizes the educational value of the concept, but not the clinical one. In this regard it states that is not require a revision of the definition, but there are necessary more research to elucidate the mechanisms of this disease [11].

In conclusion, metabolic syndrome, include lipid metabolism disorders (obesity, dyslipidemia), glucose metabolism disorders (impaired glucose tolerance or type 2 diabetes) and protein metabolism disorders (hyperuricemia) and hypertension (hemodynamic disorder with metabolic starting point). There are not included in the term of metabolic syndrome rare syndromes as achantosis nigricans, generalized lipoatrophy and lipodystrophy, telangiectatic ataxia or leprechaunism encountered especially in Africa and tropical countries.

Prevalence of metabolic syndrome

Over 25% of the adult population of the world have metabolic syndrome. The prevalence of metabolic syndrome in children and adolescents is increased parallel with the increased prevalence of obesity [12]. About 27% of American adult population have metabolic syndrome [13]. In Dolj, an epidemiological study of 2,000 subjects from rural areas showed a prevalence of 39% of MS. Between MS and type 2 diabetes mellitus (T2DM) is a very close relationship: 1/3 of people with MS has diabetes and 80-95% of adults with T2DM has MS [14, 15].

Diagnosis of metabolic syndrome

It is important to note that metabolic syndrome is a phenomenon not very clear to diagnose. It consists of a series of symptoms

that often occur together. Obesity, insulin resistance and abnormal blood lipid levels may be signs that a person suffer of metabolic syndrome.

To detect the metabolic syndrome requires a clinical examination and some blood tests commonly used to evaluate the blood pressure, lipid profile and glucose tolerance. People with metabolic syndrome must meet three of the following criteria according to the most recent consensus published in October 2009, representing the viewpoint of the International Diabetes Federation (IDF), National Heart, Lung, Blood Institute (NHLBI), American Heart Association (AHA), World Heart Federation, International Atherosclerosis Society and the International Association for the Study of Obesity (IASO):

• high plasma levels of fasting glucose (≥100mg/dl)

• elevated blood pressure (≥130/85mmHg)

• low serum concentrations of HDL-cholesterol [<40mg/dl (<1mmol/l) in men and <50mg/dl (<1.29mmol/l) in women]

• elevated serum triglycerides [≥150mg/dl (≥1.7mmol/l)]

• abdominal obesity (abdominal circumference should not even be a mandatory component continues to be considered a very useful preliminary screening tool. Abdominal circumference, ethnicity specific, in Caucasians ≥80cm in women and ≥94cm in men).

Four of the five components that make up MS have been identified as risk factors for CVD and occur more frequently in non diabetic individuals with insulin resistance/hyperinsulinemia. The relationship between excessive adipose tissue and decrease insulin-mediated glucose uptake has been demonstrated many years before [16], but, however, obesity is not equal with insulin resistance and it is necessary to understand the relationship obesity - insulin resistance - cardio-metabolic risk to see perspectively MS.

The fact that not all overweight/obese people are insulinresistant and demonstrate abnormalities associated with this defect in insulin action, has resulted in dividing these people into two groups: obese metabolically healthy and obese with metabolic abnormalities.

The fact that obese people may be sensitive to insulin does not mean that excess body fat has negative effects on insulin action and that it may increase metabolic abnormalities such as TG or low HDL-cholesterol regardless of the BMI value.

Many studies have demonstrated the degree to which components of MS varies considerably depending on the degree of insulin resistance at a certain level of fat. Thus, Ninomiya et al. [17] used data from NHANES III to examine the relationship between individual components of MS in patients with myocardial infarction (MI) and stroke. They found that insulin resistance (fasting plasma glucose >110mg/dl or a diagnosis of type 2 diabetes) and other components of MS were independent predictors of MI and stroke. In the absence of an independent report from CA and disease, the authors suggested that it has an indirect effect compared with other components of MS.

Studies have shown that abdominal obesity is an essential ingredient of the MS, claiming that "MS begins with central obesity" [18]. This statement has important clinical implications and teaching, but can be challenged. More specifically, there is evidence that the link between obesity,

measured by BMI and components of MS is comparable to that between AC and MS and that the ability of BMI to predict type 2 diabetes or cardiovascular disease is also comparable to that achieved by measuring AC. Studies have shown that "BMI and in particular AC are strongly associated with CVD and diabetes in particular."

It is obvious the importance of recognizing and addressing multiple risk factors for CVD and type 2 diabetes.

Decreased glucose tolerance and/or type 2 diabetes is one of the criteria of MS. Once an individual is diagnosed with one of the two states is important to address all risk factors for CVD. The joint report of ADA - EASD [19] put forth the hypothesis that "adults with any cardiovascular risk factor has to be identified and evaluated for the presence of other cardiovascular risk factors" and "that all cardiovascular risk factors should be individually identified and treated aggressively ".

There is a general agreement that the SM predicts the occurrence of both type 2 diabetes and CVD, being somewhat more frequently with the type 2 diabetes [20, 21]. However, it is not so clear that the MS predicts better than its individual components or DM occurrence of cardiovascular events. This should not surprise since glucose intolerance, elevated TG and/or low HDL-C and high blood pressure are known risk factors for CVD and/or diabetes type [22].

Eddy et al. [23], using the NHANES database, found that "high glucose levels are a good predictor of future risk of heart attack as any other component of MS". It is fair to conclude that the term of MS identify individuals at risk for Type 2 diabetes/BCV, but is less efficient than if it were done to identify the individual using each component of MS.

There is a general agreement that glucose intolerance, increased serum TG, low HDL-cholesterol and high blood pressure, tend to cluster together, although there are arguments to support that insulin resistance is the reason why this occurs [18, 22, 24, 25]. It is also clear that being overweight/obese increases the likelihood that this group of anomalies occurs. However, this does not necessarily mean that use of these features associated diagnosis of MS is particularly useful. Indeed, MS is relatively insufficient to provide a better approach to identify persons at risk for CVD or diabetes. Framingham score gives a much more useful to identify individuals at risk for CVD than MS. Framingham score using various factors known to predict CVD. Including capture direct link between smocking tobacco and CVD, and the fact that smokers tend to have insulin resistance, glucose intolerance and dyslipidemia, with elevated TG and low HDL-cholesterol [26, 27]. Although MS is less effective as a predictor for CVD than Framingham score, it is instead better predictor for type 2 diabetes. Specifically, glucose intolerance is one of the criteria for diagnosing MS and fasting plasma glucose is a better predictor of Type 2 diabetes than the existence of MS.

The most complete analysis of these issues was conducted by Wilson et al. [28], using data from the Framingham Offspring study that enrolled 3323 middle-aged people. For example, the relative risk (RR) of CVD in these patients ranged from 1.6 - 2.0 in the presence of any components of MS, while the risk of type 2 diabetes was increased from three to six times when IFG was present. When any two criteria were present, the RR of

CVD ranged 1.7 - 2.6, the highest risk being when it was associated with abdominal obesity and IFG. IFG together with any other four criteria for MS had the highest RR for type 2 diabetes in developing countries, ranging from 8.2 - 10.7. Finally, it was found that both two and three abnormalities present are equally useful in predicting CVD and type 2 diabetes.

Metabolic syndrome - should be treated?

Often the diagnosis of metabolic syndrome is supported, although it seems to have no direct clinical benefit, but is a useful educational tool to improve adherence and awareness of a healthy lifestyle.

Metabolic syndrome is associated with an increased risk of mortality from ischemic heart disease, other heart disease or stroke. Therefore, once discovered symptoms and diagnosis of metabolic syndrome, it is needed to control risk factors:

- Control of body weight;
- Decreased blood triglycerides;
- Control blood pressure;
- Maintaining normal blood glucose;
- Increased levels "good" cholesterol (HDL-cholesterol).

One such patient was planned to make regular medical checks. At least once a year needed a nutritionist and cardiologist consultation.

Along with the treatment prescribed by your doctor to correct metabolic disorders (hypertension, diabetes, dyslipidemia), an important role in disease control is eating. Therefore attention should be paid to diet. It is important to stop or limit consumption of foods that can aggravate metabolic disorders described and to grow food intake benefits that may improve blood values, blood glucose and blood lipids.

To control high blood pressure with medication prescribed by a doctor to be taken strictly, diet is required. It will limit salt intake and stimulating substances such as coffee and will increase intake of fruits and vegetables. To control dyslipidaemia should avoid eating fat, especially animal, replaced red meat with poultry and fish. Also, good effects on lipid profile normalization are eating foods high in mono and polyunsaturated fatty acids (omega-3), such as olive oil, canola oil.

Weight control must combine rational control diet and sedentary by physical activity daily. Along with achieving ideal weight optimization is also recommended to change lifestyle, smoking cessation and to stop alcohol abuse.

Conclusions

Metabolic syndrome even after 70 years from discovery raises the complexity of joint problems posed: metabolic disorders at all levels usually associated with cardiovascular disease. Due to the high proportion of affected people, metabolic syndrome is a current topic of interest for physicians and researchers.

In conclusion, we believe that it is not so important the diagnosis of MS but the treatment of all abnormalities that it includes is much more important.

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