

NEW CONCEPTS REGARDING THE METABOLIC SYNDROME

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REZUMAT

Noțiunea de sindrom metabolic se referă la o asociere specifică de factori de risc cardiovascular la același individ: scăderea toleranței la glucoză sau diabet zaharat, obezitate de tip abdominal, dislipidemie aterogenă, tensiune arterială crescută, rezistență la insulină, status protrombotic și proinflamator. O serie de factori par a contribui la această susceptibilitate, îndeosebi predispoziția genetică și înaintarea în vârstă. În comparație cu persoanele fără sindrom metabolic, bolnavii cu sindrom metabolic au un risc dublu de deces prin accident vascular coronarian sau cerebral și triplu de accident vascular nefatal coronarian sau cerebral. Persoanele cu sindrom metabolic au un risc de 5 ori mai mare de a dezvolta diabet zaharat de tip 2 (dacă acesta nu este încă prezent). De aceea este imperativă, din punct de vedere moral, medical și economic, identificarea precoce a persoanelor cu risc metabolic, astfel încât prin modificarea stilului de viață și prin intervenții terapeutice să se prevină apariția diabetului zaharat și/sau a bolilor cardiovasculare. Existența unor multiple definiții ale sindromului metabolic a creat confuzii, a îngreunat comparația directă între datele unor studii clinice și evaluarea prevalenței sindromului. În anul 2005, Grupul de Consens între Federația Internațională pentru Diabet și Organizația Mondială a Sănătății a elaborat o nouă definiție a sindromului, stipulând importanța obezității centrale cu modificări în funcție de grup etnic, în speranța că va fi adoptată în întreaga lume și că se va dovedi convenabilă și utilă în practica clinică și în studiile epidemiologice.

Cuvinte cheie: sindrom metabolic, definiție, epidemiologie, tratament clinic

ABSTRACT

The metabolic syndrome refers to a specific clustering of cardiovascular risk factors in the same individual: prediabetes or diabetes, abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance, a prothrombotic state, and a proinflammatory state. Several factors appear to contribute to this susceptibility, especially genetic predisposition and aging. People with metabolic syndrome are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome. People with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes (if not already present). So there is an overwhelming moral, medical and economic imperative to identify those individuals with metabolic syndrome early, so that lifestyle interventions and treatment may prevent the development of diabetes and/or cardiovascular disease. The existence of multiple definitions for the metabolic syndrome has caused confusion, has resulted in difficult direct comparisons between the data from clinical studies and assessment of syndrome prevalence. In 2005, the International Diabetes Federation and World Health Organisation Consensus Group has elaborated a new definition of the syndrome, emphasising the importance of central obesity with modifications according to ethnic group, hoping that it will be adopted worldwide and prove convenient and useful in clinical practice and epidemiological studies.

Key Words: metabolic syndrome, definition, epidemiology, clinical management

The metabolic syndrome has been referred to as the insulin resistance syndrome, metabolic syndrome X, and dysmetabolic syndrome. It consists of a specific clustering of cardiovascular risk factors in the same individual: prediabetes or diabetes, abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance, a prothrombotic state, and a proinflammatory state.

This specific clustering of cardiovascular risk factors is associated with genetic predisposition and aging. Some ethnic groups are particularly susceptible to the metabolic syndrome, but this syndrome is uncommon in the absence of obesity and physical inactivity. Insulin resistance is a common feature among the many components of metabolic syndrome and it plays a key pathogenic role.

The prevalence of metabolic syndrome is estimated to be around 20-25%.¹ People with metabolic syndrome have a twofold risk of death and a threefold risk of non-fatal coronary or vascular event compared with people without the syndrome.² The risk of developing type 2 diabetes is fivefold greater in patients with metabolic syndrome, if it isn't already present.³ As 80% of the diabetic patients die from cardiovascular disease, metabolic syndrome and diabetes represent a

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major problem for the healthcare system.⁴

Early diagnosis of the metabolic syndrome helps preventing diabetes and/or cardiovascular disease through lifestyle interventions and treatment.

Several diagnostic criteria were proposed for the metabolic syndrome. The most widely accepted of these were submitted by WHO, the European Group for the Study of Insulin Resistance (EGIR), and NCEP ATP III.⁵

According to the definition of the World Health Organization, the metabolic syndrome consists in abnormalities of glucose metabolism and/or insulin resistance together with ≥ 2 of the following disorders: raised arterial pressure $\geq 140/90$ mm Hg, raised plasma triglycerides (≥ 150 mg/dL; 1.7 mmol/L), and/or low HDL cholesterol (< 35 mg/dL, 0.9 mmol/L in men; < 39 mg/dL, 1.0 mmol/L in women), central obesity (males: waist to hip ratio > 0.9 ; females: waist to hip ratio > 0.85) and/or BMI > 30 kg/m², microalbuminuria (urinary albumin excretion rate ≥ 20 g/min or albumin/creatinine ratio ≥ 30 mg/g).¹

According to the Adult Treatment Panel III definition, the metabolic syndrome is diagnosed in the presence of any 3 of the following 5 abnormalities: (1) waist circumference ≥ 102 cm (40 in) in men or ≥ 88 cm (35 in) in women, (2) serum triglyceride levels ≥ 150 mg/dL, (3) HDL-cholesterol level ≥ 40 mg/dL in men or ≥ 50 mg/dL in women, (4) blood pressure $\geq 130/85$ mm Hg, and (5) fasting serum glucose ≥ 110 mg/dL.⁶ (Table 2)

Some other groups, such as the European Group for the Study of Insulin Resistance (EGIR) and the American Association of Clinical Endocrinology (AACE) have, at different times, presented their own criteria for the metabolic syndrome definition.^{7,8}

The prevalence of the metabolic in the adult population is estimated at 20-25%.^{9,10} There are differences according to race, gender and age.

A recent analysis presented by the Third National Health and Nutrition Examination Survey (NHANES III), indicates that about 47 million Americans (23.7% of the population) have the metabolic syndrome.¹⁰ The highest rates are observed in Hispanics (Mexican American) and the lowest rates in black men. The prevalence of the metabolic syndrome also increases with age, with a prevalence of 30% in adults about 40 years old, and 40% in adults about 60 years old.

The Strong Heart Study investigators estimated the prevalence of the metabolic syndrome in American Indians and observed that it was more than twice as high as in the NHANES population: 43.6% in men 45-49 years old as compared with 20.0% among

NHANES III men and 56.7% in women of the same age group as compared with 23.1% among NHANES III women.¹¹

People of Asian descent had a higher than average predisposition to develop the metabolic syndrome and at relatively low BMI levels.¹²

US whites of European origin appear to be more predisposed to atherogenic dyslipidemia, while US blacks of African origin are more prone to hypertension, type 2 diabetes mellitus, and obesity and Hispanics and Native Americans appear to be especially susceptible to type 2 diabetes mellitus and tend to develop hypertension less often than blacks do.¹³

The components of the metabolic syndrome have also different definitions in different countries.

In the United States, obesity in adults is defined as a body mass index (BMI) ≥ 30 kg/m², and individuals with a BMI of 25-29 kg/m² are considered overweight. Abdominal or central obesity is defined as a waist circumference ≥ 88 cm for women and ≥ 102 cm for men and has a better cardiovascular disease risk prediction than a given BMI level.¹⁴ The prevalence of obesity (BMI ≥ 30 kg/m²) appears to be increasing in all US population segments, including children.¹⁵⁻¹⁷

The degree and pattern of body fatness at a given BMI level are different in different populations. At a given BMI, there is more body fat in Asian populations compared with white American or European populations, and there is less body fat and more muscle for Pacific Islander populations.^{18,19} Asian Americans seem to gain abdominal fat preferentially. In Asian Americans and in South Asians, a substantial number of risk factors associated with the metabolic syndrome (eg, insulin resistance, hypertension, and diabetes) have been observed in individuals with BMI levels < 25 kg/m².²⁰

These multiple definitions for the metabolic syndrome have caused confusion and made it difficult to compare the data from studies where different definitions have been used to identify the syndrome.

On April 14th 2005, in Berlin, a new and clinically accessible definition of the metabolic syndrome was presented for the first time, by the International Diabetes Federation (IDF).²¹ The new definition was the result of a global consensus statement. Present at the meeting were experts in the fields of diabetes, cardiology, lipidology, public health, epidemiology, genetics, metabolism and nutrition from six continents. The new definition is based on earlier definitions proposed by the WHO and NCEP ATP III, but is easier to apply in clinical practice, as it avoids the need

for expensive measurements, that are usually used in research studies.

The IDF definition of the metabolic syndrome requires the presence of central obesity, plus two of the following four additional factors: raised triglycerides, reduced HDL cholesterol, raised blood pressure, or raised fasting plasma glucose level. For the first time, the definition of central obesity includes gender and ethnicity-specific cut-points for waist circumference. (Table 1)

Table 1. The new International Diabetes Federation (IDF) definition.²¹

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

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

plus any two of the following hour factors:

- **Raised TG level** : ≥ 150 mg% (1.7 mmol/L)

or specific treatment for this lipid abnormality

- **Reduced HDL cholesterol:**

< 40 mg% (1.03 mmol/L) in males and

< 50 mg% (1.29 mmol/L) in women

or specific treatment for this lipid abnormality

- **Raised blood pressure** : systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg,

or treatment of previously diagnosed hypertension

- **Raised fasting plasma glucose (FPG)** ≥ 100 mg% (5.6 mmol/L) ,

or previously diagnosed type 2 diabetes.

If above 100 mg% or 5.6 mmol/L, OGTT is strongly recommended but is not necessary to define presence the syndrome.

The new IDF consensus statement includes recommendations for additional criteria to be included in research and epidemiological studies of the metabolic syndrome. It considers that both abnormal abdominal fat distribution and insulin resistance are potential and inter-related causes of the metabolic syndrome.

Central (abdominal) obesity is a prerequisite risk factor for the diagnosis of the syndrome in the new definition. It can be easily assessed using waist circumference and is independently associated with each of the other metabolic syndrome components including insulin resistance.^{22,23}

Insulin resistance, which is difficult to measure in day-to-day clinical practice, is not an essential requirement.²⁴

Atherogenic dyslipidaemia is characterised as a combination of raised triglycerides (TG), low concentrations of HDL-c, elevated apolipoprotein B (ApoB), small dense LDL and small HDL particles. All of these lipidic abnormalities are independently

atherogenic.²⁵ Their combination is commonly observed in patients with type 2 diabetes. Low HDL-c and high TG levels are frequently found in patients with insulin resistance, with or without type 2 diabetes, and are risk factors for coronary heart disease (CHD).²⁶⁻²⁸

Central obesity is most easily appreciated by measuring the waist circumference. The cut-points for waist circumference are gender and ethnic group, but not country of residence specific. (Table 2) The IDF consensus group strongly recommends that, for epidemiological studies and, wherever possible, ethnic group specific cut-points should be used for people of the same ethnic group wherever they are found. For example, the criteria recommended for Japan should also be used in expatriate Japanese communities, regardless of place and country of residence.²⁹

Table 2. Ethnic specific values for waist circumference.²¹

Country/Ethnic group	Waist circumference	
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
North Americans	Male	≥ 102 cm
	Female	≥ 88 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab)	Use European data until more specific data are available	

The IDF consensus group identified a number of other parameters that appear to be related to the metabolic syndrome. (Table 3) These should be included in research studies in order to determine their predictive power for cardiovascular disease and/or diabetes. The use of these additional factors in research will also allow further modification of the definition if necessary and the validation of the new clinical definition in different ethnic groups.

In my opinion, the IDF consensus group definition of the metabolic syndrome should be adopted worldwide, as it is very clear and easy to use, both in clinical practice and in epidemiological studies. These will permit the clinical diagnosis of the

metabolic syndrome by general practitioners, an early identification of patients at considerably increased risk of developing cardiovascular disease and/or type 2 diabetes and will assess the impact of treatment of all the components of the syndrome on cardiovascular disease risk.

Table 3. Additional metabolic criteria for research.²¹

Abnormal fat distribution	General body fat distribution (DXA) Central fat distribution (CT/MRI) Adipose tissue biomarkers: leptin, adiponectin Liver fat content (MRS)
Atherogenic dyslipidemia (beyond elevated triglyceride and low HDL)	ApoB (or non-HDL-c) Small LDL particles
Dysglycemia	OGTT
Insulin resistance (other than elevated fasting glucose)	Fasting insulin/proinsulin levels HOMA-IR Insulin resistance by Bergman Minimal Model Elevated free fatty acids (fasting and during OGTT) M value from clamp
Vascular dysregulation (beyond elevated blood pressure)	Measurement of endothelial dysfunction Microalbuminuria
Proinflammatory state	Elevated high sensitivity C-reactive protein (SAA) Elevated inflammatory cytokines (TNF-alpha, IL-6) Decrease in adiponectin plasma levels
Prothrombotic state	Fibrinolytic factors (PAI-1 etc) Clotting factors (fibrinogen etc)
Hormonal factors	Pituitary-adrenal axis

RECOMMENDATIONS FOR TREATMENT

Once the diagnosis of the metabolic syndrome is confirmed, the management of this condition should be aggressive and uncompromising, in order to reduce the risk of CVD and type 2 diabetes.

Early recognition of the metabolic syndrome represents an opportunity for risk recognition, as overweight/obesity and physical inactivity are reversible and the individual components of the metabolic syndrome are also modifiable.

Management of the metabolic syndrome consists

primarily of 2 strategies: modification of the root causes and treatment of the metabolic risk factors.

Modification of the root causes includes weight reduction and increased physical activity. Treatment of the metabolic risk factors includes treatment of atherogenic dyslipidemia, elevated blood pressure, prothrombotic state, and underlying insulin resistance.

We have to keep in mind that all of the components of the metabolic syndrome may be improved with weight reduction and increased physical activity, and that until now there are no randomized clinical trials available to show a reduction in morbidity and mortality following treatment of the metabolic syndrome per se.

Theoretically, aggressive treatment to control to optimal levels elevated blood pressure and dyslipidemia in individuals with metabolic syndrome, could result in the prevention of about 80% of cardiovascular events.³⁰

It is recommended that patients with diagnosed metabolic syndrome should undergo a full cardiovascular risk assessment in conjunction with the following:

Primary intervention

The primary management for the metabolic syndrome consists in a healthy lifestyle promotion.²¹ This includes:

- moderate caloric restriction, with the goal to achieve a 5–10 % loss of body weight in the first year;
- moderate increase in physical activity;
- change in dietary composition;
- smoking cessation.

The results of Finnish and American prevention of diabetes studies have shown that a small weight loss may bring marked clinical benefits in terms of preventing or delaying by several years the conversion to type 2 diabetes in high-risk individuals with glucose intolerance who were, generally, obese.^{31,32}

Nutritional recommendations call for a low intake of saturated fats, trans fats, and cholesterol; reduced consumption of simple sugars; and increased intakes of fruits, vegetables, and whole grains. Extremes in intakes of either carbohydrates or fats should be avoided.

Regular and moderate physical exercise has been shown to improve several metabolic risk factors and is associated with a reduction in the risk of developing many chronic diseases. The standard exercise recommended is a daily minimum of 30 minutes of moderate-intensity physical activity. Progressive increase of the level of physical activity appears to

enhance the beneficial effect. In order to help the patients to initiate and maintain a regular exercise regimen, they should be advised to use multiple short (10- to 15-minute) bouts of activity (brisk walking), avoiding common sedentary activities in leisure time (television watching and computer games). They may purchase simple exercise equipment for the home (eg, treadmills) and add regular exercise into daily schedule (eg, brisk walking, jogging, swimming, biking). More exercise (1 hour daily) is even more efficacious for weight control.

Secondary intervention

In case lifestyle changes are not efficient enough and in patients at high risk for CVD, drug therapy is required to treat the metabolic syndrome. We do not know yet whether we have to treat the underlying mechanisms of the metabolic syndrome as a whole or to treat the individual components of the syndrome and thereby to reduce the impact of all these risk factors on metabolic and cardiovascular consequences. It is expected that a reduction in the individual risk will reduce the overall impact on CVD and diabetes risk.

Atherogenic Dyslipidemia

Associated with lifestyle modification, several drugs may be considered in patients with atherogenic dyslipidemia. As emphasized by ATP III, the primary target of lipid lowering therapy is the reduction of LDL cholesterol. Several clinical trials have confirmed the benefit of statin therapy.⁶ Fibrates also improve all components of atherogenic dyslipidemia and reduce the risk for CVD.²⁸ In special circumstances, the combination of fibrates with statins may be useful, but with a higher risk for myopathy.³⁴ There are many reports of severe myopathy occurring from the combination of statin plus gemfibrozil. Gemfibrozil interferes with catabolism of statins in the liver, which can raise statin blood levels, thereby predisposing to myopathy. Fenofibrate, which does not adversely interact with statin catabolism, may be safer to use in combination therapy. Combination of nicotinic acid with statins may also be promising in patients with metabolic syndrome. Higher doses of nicotinic acid can raise plasma glucose levels. Therefore, if nicotinic acid is used in patients with impaired glucose metabolism, its dose should be kept relatively low (eg, 1 to 2 g per day).³⁵

Elevated Blood Pressure

No particular antihypertensive agents have been identified as being preferable for hypertensive patients with metabolic syndrome, but some of them should be avoided, because of metabolic adverse effects. For example, diuretics and beta-blockers may worsen

insulin resistance and atherogenic dyslipidemia. For thiazide diuretics, doses should be kept relatively low in accord with current recommendations. Beta-Blockers are cardioprotective in patients with established coronary heart disease and are no longer contraindicated in patients with type 2 diabetes. We should choose betablockers that do not increase insulin resistance and are neutral on lipid metabolism, e.g. Carvedilol or Nebivolol. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are useful antihypertensive drugs, and some clinical trials suggest that they would have 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 alone.³⁵

Insulin Resistance and Hyperglycemia

There are some interesting theories that suggest that using drugs that reduce insulin resistance one could delay the onset of type 2 diabetes and reduce CVD risk in patients with metabolic syndrome. Metformin therapy in patients with prediabetes prevented or delayed the development of diabetes, as shown by The Diabetes Prevention Program. Data regarding the use of the thiazolidinedione troglitazone, a PPAR- γ nuclear receptor agonist, suggested a similar effect, but this drug has been withdrawn from commercial use. Although insulin resistance is associated with increased CVD risk, neither metformin nor any of the thiazolidinediones now on the market have been shown to reduce the risk of CVD in those with the metabolic syndrome, prediabetes, or diabetes.³⁵

Until now, no evidence is available to support the theory that the management of insulin resistance with insulin-sensitizing agents in the absence of diabetes would reduce CVD risk. That's why these drugs can't be recommended for anything other than their glucose-lowering action.

The main therapeutic goal remains the good glycemic control, by lifestyle changes and, if necessary, by drug therapy. There is evidence suggesting that a reduction in A1C level to 7.0% or less will reduce CVD events.

Prothrombotic State

The prothrombotic state in patients with the metabolic syndrome is characterized by elevations of fibrinogen, PAI-1, and possibly other coagulation factors. However, these are not measured routinely in clinical practice. The risk for thrombotic events can be reduced by aspirin therapy. The AHA currently recommends use of aspirin prophylaxis in most patients whose 10-year risk for CHD is about 10%

as determined by Framingham risk scoring, including patients with metabolic syndrome.³⁶

Proinflammatory State

This condition is characterized by elevated cytokines (eg, tumor necrosis factor- α , and interleukin-6) as well as by elevations in acute-phase reactants (CRP and fibrinogen).

C-reactive protein (CRP), a sensitive and reliable marker of inflammation and cardiovascular risk, is regulated by proinflammatory cytokines, especially IL-6.

CRP levels tend to be higher than normal in patients with the metabolic syndrome. An elevated CRP (over 3 mg/L) is an emerging risk factor for CVD.⁶ The AHA and Centers for Disease Control and Prevention (CDC) suggest the need for CRP determination in all patients with metabolic syndrome, in order to assess their cardiovascular risk.³⁷ The purpose of CRP testing in an intermediate-risk patient (10-year risk for CHD in the range of 10% to 20%) is to find those with high CRP levels whose risk category should be raised to high. In these patients, the recommendations are to intensify lifestyle therapies, to use low-dose aspirin, and to set lower LDL goals.

AHA/CDC guidelines emphasize that CRP testing still remains optional and is not recommended routinely, because the magnitude of its independent predictive power remains uncertain.³⁸

Regarding the therapeutic options of the metabolic syndrome, I would like to mention the new generation of dual PPAR agonists which interact with both PPAR alpha and gamma receptors, thereby combining lipid and glycaemic effects. Some of these combined PPAR agonists are presently being examined in phase II and III trials, such as muraglitazar and tesaglitazar. However, safety parameters should be carefully monitored such as weight gain, heart failure induction and even carcinogenesis in rodents. To overcome these unfavourable effects, several laboratories are now focusing on partial PPAR α/γ activators, which may combine the beneficial metabolic effects with fewer undesirable side effects.

Potential future therapies for the metabolic syndrome include incretin mimetics, dipeptidyl peptidase IV inhibitors, protein tyrosine phosphatase 1B inhibitors, and endocannabinoid receptor blocking agents.²¹

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