11

Dysmetabolic Syndrome

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1. Introduction

The dysmetabolic syndrome (DMS) reunites a cluster of interrelated and important risk factors and/or medical conditions or disorders which act and worsen each other, aggravate and provoke each other, promoting the development of atherosclerotic vascular disease and type 2 diabetes (DM).

Although it has been termed „a syndrome or a disease-state", the prevalence of metabolic syndrome has risen dramatically in all societies over the past two decades; therefore, DMS should be analyzed as „an educational concept that focuses attention on complex multifactorial health problems", but in relation „to four key areas: pathophysiology, epidemiology, clinical work and public health" (Ford et all., 2002; Simmons et all., 2010). This aspect must be well deepened by doctors and understood by patients, because the patients with DMS are at a much higher risk for many and serious medical conditions (atherogenic dyslipidemia, elevated blood pressure, elevated plasma glucose, proinflammatory and prothrombotic states, and so on).

This review evaluates the multiple similarities and differences between several concepts and definitions of DMS, in an attempt to clarify its practical and clinical usefulness, amid many exciting controversies. The clinical significance of DMS, as a distinct entity, has been debated in the past years. Initially, DMS was scarcely used as a practical tool for clinical management, educational concept or pre-morbid condition, until 1988, when GM Reaven brought it to the attention of clinicians and theorists in "Banting Lecture"; thus, GM Reaven remains the main author who has developed and strengthened this „clinical and pathological concept", identifying insulin resistance as the central pathophysiologic feature (Reaven, 1988).

DMS is known under many names: „Metabolic syndrome" (World Health Organisation [WHO], 1998; National Cholesterol Education Program [NCEP], 2002; International Diabetes Federation [IDF], 2005), „Insulin resistance syndrome", „Dysmetabolic syndrome", „Cardiometabolic syndrome", „Syndrome X" (Reaven, 1988), „Plurametabolic syndrome", „Deadly Quartet: upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension" (Kaplan, 1989), "Atherometabolic Syndrome", „Sindrom dismetabopres" (Buşoi G, 2005), „CHAOS" (in Australia), and so on.

2. History

The history of DMS was not an easy one; we will present, in chronological order, the most important events (Isomaa et al., 2001).

Between 1920-1923, Kylin (as cited in Lau, 2009), a Swedish physician, described for the first time a constellation of metabolic disturbance and the clustering of hypertension, hyperglycemia, and gout. After Kylin, J Vague, from the University of Marseille, reported that body fat topography, respectively upper-body obesity, causes the predisposition to diabetes mellitus, atherosclerosis, gout, and renal calculi, and that its anatomical distribution differs according to gender. Vague used the term "android obesity" to define the pattern of fat distribution with an accumulation of adipose tissue over the trunk and the term "gynoid obesity" for adipose tissue that accumulates mostly around the hips and thighs, commonly found in women (Vague et al., 1947). As the research continued, after 1960, a link between obesity, insulin-resistance and related complications was suggested. Albrink and Meigs reported an association between trunk fat and hypertriglyceridemia (Meigs et al., 2003). In 1975-1977, Haller used the term "metabolic syndrome" for an association of obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia, and hepatic steatosis, and describes the additional role of these risk factors on the cardiovascular disease (CVD) (Haller, 1977). In 1977-1978, Singer and Phillips developed the concept that risk factors for myocardial infarction, respectively a "constellation of associated abnormalities" (i.e. glucose intolerance, hyperinsulinemia, hypercholesterolemia, hypertriglyceridemia, and hypertension) are associated with CVD, aging, obesity, sex hormones, and other clinical states (Singer, 1977; Phillips, 1978). In 1988, Reaven, describes "Syndrome X" in his famous Banting Lecture; this is a critical moment, subject to many controversies in the literature; more and more risk factors (RF) (hypertension, hyperglycemia, glucose intolerance, elevated triglycerides, and low HDL-cholesterol), as well as many metabolic disturbances, especially insulin resistance, are incriminated in the pathogeny of CVD (Reaven, 1988). In 2005, Kahn draws attention to several unresolved questions about the metabolic syndrome, many of them still unresolved even now:

- Metabolic syndrome name?
- Existence of metabolic syndrome?
- More than some of its parts?
- Metabolic sindrome vs. prediabetes & type 2 diabetes
- Diagnostic utility? Pathogenesis? Clinical utility?

3. Definitions of dysmetabolic syndrome

In 1998-1999, WHO defines metabolic syndrome (MS) as a clustering of arterial hypertension, dyslipidemia, obesity with high waist to hip ratio, microalbuminuria, glucose intolerance or insulin resistance, or type 2 diabetes; at the same time, it recognizes „CVD as the primary outcome of the metabolic syndrome'' (table 1).

The criteria for the diagnosis of MS are: the presence of one of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND two of the following:

1. blood pressure ≥ 140/90 mmH
2. dyslipidemia: triglycerides (TG) ≥ 1.695 mmol/L and high-density lipoprotein cholesterol (HDL-C) ≤ 0.9 mmol/L (in males) or ≤ 1.0 mmol/L (in females);

Parameters	NCEP ATP3 2005	IDF 2005	EGIR 1999	WHO 1999	AACE 2003
Required		Waist ≥94 cm (men) or ≥80 cm (women)*	Insulin resistance or fasting hyperinsulinemia in top 25 percent	Insulin resistance in top 25 %•; glucose ≥6.1 mmol/L (110 mg/dL); 2-hour glucose ≥7.8 mmol/L (140 mg/dL)	High risk of insulin resistanceΔ or BMI ≥25 kg/m^2 or waist ≥102 cm (men) or ≥88 cm (women)
Nr. of abnormalities	≥3 of:	And ≥2 of:	And ≥2 of:	And ≥2 of:	And ≥2 of:
Glucose	≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	≥5.6 mmol/L (100 mg/dL) or diagnosediabetes	6.1-6.9 mmol/ (110-125 mg/dL)		≥6.1 mmol/L (110 mg/dL); ≥2-hour glucose 7.8 mmol/L (140 mg/dL)
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL-C◊	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL-C	<1.0 mmol/L (40 mg/dL)	<0.9 mmol/L (35 mg/dL) (men); <1.0 mmol/L (40 mg/dL) (women)	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women)
TGs	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides◊	≥1.7 mmol/L (150 mg/dL) or drug treatment for high TGs	or ≥2.0 mmol/L (180 mg/dL) or drug treatment for dyslipidemia	or ≥1.7 mmol/L (150 mg/dL)	≥1.7 mmol/L (150 mg/dL)
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)§		Waist ≥94 cm (men) or ≥80 cm (women)	Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m^2	
HTA	≥130/85 mmHg or drug treatment for HTA	≥130/85 mmHg or drug treatment for HTA	≥140/90 mmHg or drug treatment for hypertension	≥140/90 mmHg	≥130/85 mmHg

* For South Asia and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); for Japanese patients, waist ≥90 cm (men) or ≥80 cm (women).
• Insulin resistance measured using insulin clamp.
Δ High risk of being insulin resistant is indicated by the presence of at least one of the following: diagnosis of CVD, hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease or acanthosis nigricans; family history of Type 2 diabetes, hypertension of CVD; history of gestational diabetes or glucose intolerance; nonwhite ethnicity; sedentary lifestyle; BMI 25 kb/m2 or waist circumference 94 cm for men and 80 cm for women; and age 40 years.
◊ Treatment with one or more of fibrates or niacin. § In Asian patients, waist ≥90 cm (men) or ≥80 cm (women).

Table 1. Five current definitions of the metabolic syndrome (Meigs, 2006).

3. central obesity: waist:hip ratio > 0.90 (in males) and > 0.85 (in females), or body mass index > 30 kg/m2 ;
4. microalbuminuria: urinary albumin excretion ratio ≥ 20 μg/min. or albumin:creatinine ratio ≥ 30 mg/g.

We can see a potential disadvantage of the WHO criteria, namely the need for the routine assessment of the glycemic metabolism. (Simmons et al., 2010; Alberti & Zimmet, 1998).

The European Group for the Study of Insulin Resistance (EGIR, 1999), designed to be used in non diabetics only, requires two or more of the following:

1. central obesity: waist circumference ≥ 94 cm (male), ≥ 80 cm (female);
2. dyslipidemia: TG ≥ 2.0 mmol/L and/or HDL-C < 1.0 mmol/L or treated for dyslipidemia;
3. hypertension: blood pressure ≥ 140/90 mmHg or antihypertensive medication;
4. fasting plasma glucose (FPG) ≥ 6.1 mmol/L (table 1).

In 2001-2002, the National Cholesterol Education Program and Adult Treatment Panel (ATPIII) provides a clinical definition of metabolic syndrome, "a multiplex risk factor for cardiovascular disease (CVD) and identifies" six components of the metabolic syndrome that relate to CVD: abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance ± glucose intolerance, proinflammatory state, prothrombotic state". It also states that "the presence of type 2 DM does not exclude a diagnosis of metabolic syndrome" and the definition does not require evidence of insulin or glucose abnormalities, although „abnormal glycemia is one of the criteria". The US NCEP and ATP III require at least three of the following:

1. central (abdominal) obesity: waist circumference ≥ 102 cm (40 inches) (male), ≥ 88 cm (35 inches) (female);
2. dyslipidemia:
   - TG ≥ 150 mg/dL (1.7 mmol/L), or drug treatment for elevated triglycerides;
   - HDL-C < 40 mg/dL (1 mmol/L) (male), < 50 mg/dL (1,3 mmol/L) (female), or drug treatment for low HDL-C;
3. blood pressure ≥ 130/85 mmHg, or drug treatment for elevated blood pressure;
4. FPG ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose (table 1).

We can see that:

- the WHO criteria consider both central obesity ("waist-to-hip ratio") and overall obesity (defined by the "BMI");
- the NCEP ATP III criteria consider only central obesity ("waist circumference"),
- the presence of type 2 DM does not exclude the diagnosis of metabolic syndrome;
- elevated microalbuminuria is a component in the WHO definition, while it is not considered for NCEP ATP III (NCEPT ATPIII, 2001, 2002).

In 2005, ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes) discourage the use of the term "metabolic syndrome" in the field literature, questioning "whether this constellation of clinical findings constitutes a syndrome" and "whether that constellation, in and of itself, is an entity of medical concern above and beyond the individual components", and so on (Beaser & Levy, 2007).

The IDF (International Diabetes Federation) releases in 2005 the "Consensus worldwide definition" of the metabolic syndrome, which mentions the following criteria needed for the diagnosis:

1. central obesity is an essential element (defined as waist circumference with race/ethnicity specific values) and any two of the following:
2. raised triglycerides: > 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality;
3. reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality;
4. raised blood pressure: systolic BP > 130 mmHg or diastolic BP >85 mmHg, or treatment of previously diagnosed hypertension;
5. raised fasting plasma glucose : > 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes. (table 1 and 2).

It can be noted that:

- if FPG > 5.6 mmol/L or 100 mg/dL, oral glucose tolerance test (OGTT) is strongly recommended, but is not necessary to define presence of the MS;
- if BMI is > 30 kg/m², central obesity can be assumed and waist circumference does not need to be measured (Alberti et al., 2005, 2006).

ADDITIONAL METABOLIC IDF CRITERIA (for research)
Abnormal body fat distribution: - general body fat distribution, - central fat distribution (CT/MRI), - adipose tissue biomarkers: leptin, adiponectin, - liver fat content.
Atherogenic dyslipidaemia (beyond elevated triglyceride and low HDL): - ApoB (or non-HDL-C), - small LDL particles.
Dysglycaemia: Oral glucose tolerance test (OGTT).
Insulin resistance (other than elevated fasting glucose): - fasting insulin/proinsulin levels, - insulin resistance, - elevated free fatty acids (fasting and during OGTT).
Vascular dysregulation (beyond elevated blood pressure): - measurement of endothelial dysfunction, - microalbuminuria.
Proinflammatory state: - elevated high sensitivity C-reactive protein, - elevated inflammatory cytokines (eg 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.

Table 2. IDF: Additional metabolic criteria (for research) -„platinum standard" definition (www.idf,org)

After a brief period of time, AHA (American Heart Association) and NHLB (National Heart, Lung, and Blood Institute) state the opposite and consider MS:

- a "multidimensional risk condition" for both atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes;
- as "multiple risk factors that are metabolically interrelated";
- as "multifactorial in origin, with underlying causes and exacerbating factors".

The confusion generated by AHA/NHLBI is clarified by AHA/Updated NCEP ATP III, which gives the following criteria of diagnosis:

1. elevated waist circumference:
   - men — greater than 40 inches (102 cm);
   - women — greater than 35 inches (88 cm);
2. elevated triglycerides - equal to or greater than 150 mg/dL (1.7 mmol/L);
3. reduced HDL ("good") cholesterol:
   - men — less than 40 mg/dL (1.03 mmol/L);
   - women — less than 50 mg/dL (1.29 mmol/L);
4. elevated blood pressure:
   - equal to or greater than 130/85 mm Hg or
   - use of medication for hypertension;
5. elevated fasting glucose:
   - equal to or greater than 100 mg/dL (5.6 mmol/L) or use of medication for hyperglycemia.

The following notes are made:

- lowering the threshold for abnormal fasting glucose to 100 mg/dL, corresponding to the ADA criteria for impaired fasting plasma glucose;
- the inclusion of diabetes in the hyperglycemia trait definition;
- the therapeutic control of dyslipidemia and arterial hypertension (table 1) (Grundy et al., 2004, 2005; Beilby, 2004).

Following this statement, AACE (American Association of Clinical Endocrinologists) propose a "third set of clinical criteria for the insulin resistance syndrome", in fact ''a hybrid of those of ATP III and WHO metabolic syndrome'', but with „clinical value as a diagnosis".

As a disease entity, MS is recognized by the American Society of Endocrinology, NCEP, and WHO, among others. The above mentioned set has some complicated aspects:

- it does not state the number of RF;
- the diagnosis is left to clinical judgment;
- the term „insulin resistance syndrome" is not applied when the patient has MD, but „high risk of being insulin resistant" is indicated by the presence of at least one of the following:
  - diagnosis of CVD, hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease or acanthosis nigricans;
  - family history of type 2 diabetes, hypertension or CVD;
  - history of gestational diabetes or glucose intolerance;
  - non-white ethnicity; sedentary lifestyle; BMI 25 kb/m2 or waist circumference 94 cm for men and 80 cm for women; and

- age 40 years (table 1) (Kahn, 2005).

Now the DMS has been recognized as a proinflammatory, prothrombotic state, with elevated levels of C-reactive protein, interleukin (IL)-6, and plasminogen activator inhibitor (PAI)-1, and so on. Therefore, in the near future, many other diagnostic criteria will arise; for example, if high-sensitivity c-reactive protein (hs-CRP) can be used as a marker to predict coronary vascular diseases in DMS and as a predictor for non-alcoholic fatty liver disease, in correlation with serum markers that indicate the disturbance of the lipid and glucose metabolism (Kogiso et al., 2009).

These sets of defining criteria for DMS are similar but they also have many important differences (clinical, etiopathogenic, ethnical, geographical, and so on) (tables 1,2,3). In fact, these five definitions of DMS illustrate "its complexity and heterogeneity", although they are not unanimously accepted.

ATP III / IDF
Atherogenic dyslipidemia Elevated blood pressure Elevated plasma glucose Prothrombotic state Proinflammatory state
ADA / EASD
Atherogenic dyslipidemia Prediabetes Elevated plasma glucose Prothrombotic state Proinflammatory state

Table 3. Clustering or constellation of the metabolic risk factors (3+) in definition of the metabolic syndrome

The DMS is an insulin-resistant state with a cluster of cardiovascular risk factors, including various combinations and substantial additional CV risk, which occur in the same individual, but the question is "how to integrate the DMS into concepts of insulin resistance, pre-diabetes, and type-2 diabetes". Insulin resistance is a component of obesity, it favors the onset of type 2 DM and is found in many cases of hypertension and hypertriglyceridaemia with low levels of HDL-cholesterol (Reaven, 1988), in association with correlated metabolic abnormalities recognized as CV risk factors that are present prior to the onset of diabetes. If insulin resistance evolves with many other characteristics (abdominal obesity, dyslipidemia, hypertension, non-dipper pattern of blood pressure, salt sensitivity, glucose intolerance, history of gestational DM, increased PAI-1/ platelets and so on), can all of these be seen as cardiovascular RF in various combinations? Which and how many of these RF carry the greatest impact? (Johnson & Weinsstock, 2006).

In all definitions of DMS, the abdominal adiposity is underlined and not the body weight. It is indeed the visceral adipocytes that are metabolically active, leading „to elevated plasma free fatty acids that result in elevated triglycerides and lower HDL cholesterol, and contribute to elevated plasma glucose"; is this explication enough to consider that this type of obesity is the RF with the greatest impact? (Beaser & Levy, 2005).

In addition to age, race, and weight are there other RF associated with an increased risk of DMS? Indeed, in NHANES III trial, other RF have emerged (postmenopausal status, smoking, low household income, high carbohydrate diet, no alcohol consumption, and physical inactivity); should these RF be included in the DMS? And when other RF for CVD will arise, which RF will not be components of the DMS? We should not forget that the notion of DMS ignores „other several strong risk factors" for cardiovascular disease (like cigarette smoking and elevated levels of low-density lipoprotein cholesterol, for example). (Palaniappan et al., 2004).

Is the treatment of the DMS different, next to the treatment for each of its components? It is obvious that the presence of a DMS component will lead to its evaluation and optimal treatment, but it is also important to look for and evaluate all the individual components of DMS from all the definitions. If a patient has certain characteristics included in one of the definitions for DMS (large waist circumference, high triglycerides and high fasting glucose) and another patient has other characteristics (high blood pressure, low HDL, and high triglycerides), both of them will be diagnosed with DMS, but will they benefit from different therapeutic strategies? Because there is no unique mechanism for DMS, thereby there won't be a unique treatment (Bayturan et al., 2010).

If we accept that "the Framingham score for the risk" is a better "short-term" (10 year) risk tool, does it mean that the metabolic syndrome was meant to identify individuals at "higher long-term risk"? Are there other risk factors for CVD, which are not components of the metabolic syndrome, such as inflammatory markers, which may have equal or greater bearing on risk? (Grundy, 2006). Is the CVD risk associated with the metabolic syndrome higher than the sum of its individual components? (Sundstorm et al., 2006).

The setting of diagnostic criteria for DMS is very difficult with numerous controversies and uncertainties. Therefore, is the DMS:

1. a true syndrome?
2. a simple collection of things with "an identifiable pattern" ?
3. a clustering of certain signs and symptoms that tend to occur under certain circumstances?
4. three or more related diagnostic entities associated with any morbid process? And so on (Kahn et al., 2005; Balta, 2010).

This research showed that the SM is a most complex problem, a focus of much research and clinical interest, involving:

- symptoms that are associated,
- diseases that occur as a result of this condition,
- multiple risk factors representing the factors of metabolic origin (table 4).

Metabolic syndrome affects 44% of the U.S. population older than age 50; the percentage of women having the syndrome is higher than that of men; the age dependency of the syndrome's prevalence is seen in most populations around the world. The „clustering" of CV and metabolic abnormalities in the same person will lead to an additional CV risk „over and above the sum of the risks associated with each abnormality" (Golden et al, 2002).

Thus, it is necessary:

- to define and validate a „single, universally accepted diagnostic tool";
- to adopt a „global and practical consensus" for using a single "adequate terminology that will guarantee the correct understanding of the etiopathogeny, morphological and metabolic substrate of the multiple complex phenomena of cardiometabolic syndrome";
- to realize a comprehensive "platinum standard" list of criteria, which could be easily used in clinical practice and be sufficiently comprehensive in the following clinical trials.

CLINICAL SYNDROMES ASSOCIATED WITH INSULIN RESISTANCE
Type 2 diabetes
CVD
Essential hypertension
Polycystic ovary syndrome
Nonalcoholic fatty liver disease
Certain forms of cancer
Sleep apnea

Table 4. Clinical syndromes associated with insulin resistance

4. Etiopathogeny of dysmetabolic syndrome

Endothelial dysfunction (ED) is a key event in the pathogenesis of atherosclerosis. The possibility of early identification of individuals at risk and achieving an objective control of the effectiveness of treatment in clinical practice become an attractive goal of therapeutic strategies useful to reduce cardiovascular morbid-mortality, and the endothelium is the logical "window" for the next evolution of atherosclerosis.

Given that DMS includes „an atherogenic dyslipidaemia, an insulin resistance state leading to a disturbed plasma glucose/insulin homeostasis, a abdominal obesity, especially visceral obesity, a thrombotic and inflammatory profile, as well as an endothelial dysfunction could substantially increase the risk of coronary heart disease (CHD) and type 2 diabetes" (Alexander et al., 2003; Kahn R, et al., 2005; Grundy, 2006).

K. Watson draws attention to the practicality of cardiometabolic risk management, particularly attractive to lower morbidity and mortality but also the economic costs for health, particularly if the disease or diseases and/or it's complications are identified early, especially in the subclinical phase (Watson, 2007).

The key to identification of cardiometabolic risk is the recognition that a patient with one or 2 clinically evident risk factors likely has additional factors, as these risk factors have been shown to „cluster"; this cluster effect is not specific for DMS; it remains a concept on the basis of which the results of future research will show new perspectives.

Meigs et al. refined the concept of the metabolic syndrome "by outlining the function of distinct clusters of risk factors", actually "three factors underlie the clustering of risk variables", risk factors that are still topical:

1. a "metabolic" factor, including BMI, waist circumference, 2-hour glucose tolerance, triglycerides, insulin sensitivity, and plasminogen activator inhibitor;

2. an "inflammation" factor, including BMI, waist circumference, fibrinogen, C-reactive protein, and insulin sensitivity ; and
3. a "blood pressure" factor, including systolic and diastolic blood pressure)" (Meigs et al., 1997).

Wilcox, presenting the much-disputed „Z syndrome" still in the concept of „cluster", cautions that „in populations at risk of vascular disease, many patients who experience a cardiovascular event either do not have identifiable risk factors or have disease severity which appears to be out of proportion to their known risk factors. Since these risk factors have been shown to be independent predictors of adverse events, they will show at least additive effects in combination and possibly potentiate each other" (Wilcox et al., 1998).

The metabolic syndrome „is a cluster of the most dangerous heart-attack risk factors:

- diabetes and pre-diabetes,
- abdominal obesity,
- high cholesterol and
- high blood pressure".

The clustering of CVD risk factors that marks the metabolic syndrome is now considered to be „the driving force for a CVD epidemic" (Stern et al., 2004).

The exact mechanisms of the complex syndrome are not yet completely known and elucidated. Presently, the main etiologic factors for DMS obesity and the dysfunctional adipose tissue are present in clinical situations determined by insulin resistance; this process also „prevents the efficient conversion of food into energy because of a vastly reduced number of insulin receptors on the cell wall", thus inducing „an increase in blood levels of insulin". In addition, there is a multiple „set of risk factors" that commonly appear together in MS, but confer „a substantial additional CV risk, over and above the sum of the risks associated with each abnormality" (Golden et al., 2002).

The etiopathogenesis of the DMS is not entirely known and understood.

There are three potential etiological categories: obesity and disorders of adipose tissue, insulin resistance and a number of independent factors that mediate specific components of the DMS;

It is an established fact that "all components of metabolic syndrome are strongly interconnected and so they cannot be treated separately".

Questioning if and when "the whole is greater than the sum of its parts?" and „what factors comprise the syndrome?", Kahn argue with several answers:

- „diagnosing the metabolic syndrome adds nothing beyond each individual risk factor for predicting cardiovascular disease or diabetes";
- „the definition should include all the factors clearly associated with that underlying pathophysiology, such that there is little ambiguity regarding the etiology of the clustering";
- "if the etiology is unclear, it becomes much more difficult to decide what factors to include in the definition, since the word "cluster" itself can be ambiguous" (Kahn et al., 2005).

There is debate "whether obesity or insulin resistance are the causes of the DMS or if they are consequences of a more far-reaching metabolic derangement".

The multiple risk factors represent factors of metabolic origin, and can be grouped in several syndromes, each of which are metabolic risk factors;

Both insulin resistance and central obesity are considered significant factors. It is necessary to specify that insulin resistance is not synonymous with type 2 diabetes mellitus. Insulin resistance is not a disease, but remains the "primary mediator of metabolic syndrome". Insulin resistance does not necessarily lead to the clinical syndromes or to obesity; obesity is a „physiologic variable that increases the likelihood that an individual will be insulin resistant". It appears long before the diagnosis of diabetes and suggests an increased risk for the latter. Unlike type 2 diabetes, in the case of insulin resistance, the pancreas produces too much insulin as a compensatory mechanism and does not require drug treatment, but only diet and exercise. The combination of insulin resistance with compensatory hyperinsulinemia will determine an increased risk for CVD (table 4, 5) (Nakamura et al., 1994; Nesto, 2003, Matsuzawa et al., 2002). Present studies maintain „the central obesity and insulin resistance" as „main etiological factors" in DMS (Matsuzawa et al., 2002).

Fasting insulin (Insulin Assay):	10 IU/mL and below is optimal; over 10 IU/mL is high.
High sensitive CRP (C-Reactive Protein):	Less than 1.0 µU/ml is optimal.
Triglycerides:	50-100 mg/dL is optimal, 100-150 mg/dL is moderate and over 150 mg/dL is high.
Homocysteine:	Less than 6 µmol.L is optimal; greater than 9 µmol/L is high.
Cholesterol:	HDL 40 mg/dL is good, although higher is even better. In studies, women with HDL of 70 mg/dL had low cardiac risk. LDL of less than 100 mg/dL is good. Total cholesterol should be less than 200 mg/dL or under.
Fasting glucose:	Normal is 74-106 mg/dL. Values of 100-125 mg/dL are indicative of Pre-Diabetes. Values greater than or equal to 126 mg/dL are indicative of Type 2 Diabetes.
Oral glucose tolerance (with 75 gr. Glucose load):	Results greater than or equal to 200 at 2 hours following the oral glucose tolerance test indicate Type 2 Diabetes.
(PAI -1):	Greater than 31
Fibrinogen:	This test is a general measure of inflammatory processes; the results vary greatly with the patient's age, gender and test method. Results that are both too high and too low are problematic.

Table 5. Lab exams in DMS (Grundy et al., 2005)

4.1 Central obesity

It has been demonstrated that the central obesity is by far the most prevalent form of the MS and a major component of the MS. Reaven points out that insulin resistance does not cause obesity; rather, obesity causes insulin resistance and has a key role in the pathophysiology of metabolic disorders; but insulin resistance also occurs in 10% to 15% of people who are not overweight. Basically, abdominal (visceral) obesity:

- represents the accumulation of central fat,
- plays a key role in the pathophysiology of metabolic disorders,
- has potential negative effects on metabolic and CV risk,
- is associated with insulin resistance, but is independently associated with each of the other MS components, including insulin resistance,
- predicts the development of type 2 DM,
- is easily measured, either by waist circumference or by waist-to-hip ratio;
- this measurement estimates the CV risk (table 3)
- has "remarkable heterogeneity"(Weisberg et al., 2003; Nesto, 2003; Grundy et al., 2005).

These affirmations are sustained by the following arguments:

- there is a linear correlation between waist circumference and visceral fat; but, subcutaneous fat is metabolically and cardiovascularly inert, exerting a possible protective function;
- insulin resistance of visceral fat is linked to dislipidemia, hypertension, hyperglycemia and inflammation, complex phenomenon representing DMS ;
- adipocyte (fat cells of the visceral fat) dysfunction may be either „intrinsic or secondary to immune dysregulation, inflammation, hypothalamic-pituitary adrenal dysfunction, local glucocorticoid dysregulation within visceral fat, or, possibly, stress or energy imbalance"; adipocytes hypertrophy is followed by macrophage infiltration, inflammation, and so on, with the alteration of different functions (TNFα, resistin, PAI-1, etc.), which contributes to a prothrombotic state;
- hypoadiponectinemia has been shown to increase insulin resistance, and is considered to be a risk factor for developing and worsening MS;
- the visceral, abdominal fat tissue releases inflammatory cytokines that increase insulin resistance in the body's skeletal muscles, and is also associated with a decreased production of adiponectin, which is the adipose-specific, collagen-like molecule with anti diabetic, anti-atherosclerotic and anti-inflammatory functions;
- TNFα presence can increase production of inflammatory cytokines and may lead to insulin resistance during a very complex process. (Grundy et al., 2004; Matsuzawa et al., 2004a, 2004b).

The distribution of adipose tissue appears to affect its role in metabolic syndrome. While visceral, intra-abdominal fat correlates with inflammation, subcutaneous fat does not. Only abdominal fat produces potentially harmful levels of cytokines (tumor necrosis factor, adiponectin, leptin, resistin, and plasminogen activator inhibitor). Only visceral fat accumulation and insulin-resistance have been associated with a cluster of dyslipidaemic features (i.e., elevated plasma triglyceride, increased very low density lipoprotein /VLDL, presence of small dense LDL particles, with decreased of HDL-cholesterol, and so on).

In conclusion, central obesity:

1. is independently associated with each of the other metabolic syndrome components, including insulin resistance
2. contributes to hypertension, dyslipidemia (high serum cholesterol, low HDL-c) and hyperglycemia, and is independently associated with higher CVD risk. (Anderson et al., 2001; Zimmet et al., 2001).

The increased flow of free fatty acids through the liver leads to accelerated synthesis of VLDL-C, hypertriglyceridemia, endothelial dysfunction, and vasoconstriction, leading to an increase in blood pressure; also, through this mechanism, insulin resistance may exert an atherogenic effect (Fonseca, 2005).

4.2 Inflammation

A number of markers of systemic inflammation, including C-reactive protein, are often increased, as are fibrinogen, interleukin 6 (IL–6), tumor necrosis factor-alpha (TNFα), and others.

CVD and diabetes are associated with elevated levels of inflammatory biomarkers, including C-reactive protein (CRP).

At the same time, CRP is the best-studied inflammatory marker of atherothrombotic risk, placed among the parameters used in "Framingham Risk Score".

C-reactive protein is present in the MS; its plasma levels increase with the number of metabolic risk factors, and also with other inflammatory markers; these associations are „purely correlative, not causative, and do not imply a mechanistic action" (table 2)

The mechanisms that lead to the increase of CRP are complex and only partially understood; we take this opportunity to remind that only excessive fatty tissue releases inflammatory cytokines and determines higher CRP levels; adipose cell enlargement and infiltration of macrophages into adipose tissue will lead to the release of proinflammatory cytokines and promote insulin resistance. It increases the thrombogenicity of circulating blood, in part by raising plasminogen activator type 1 and adipokine levels, and it causes endothelial dysfunction (Grundy et al., 2004; Ridker et al., 2004).

4.3 The prothrombotic and proinflammatory states

The prothrombotic and proinflammatory states may be metabolically interconnected by "plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen", "in response to a high-cytokine state" (Grundy et al., 2004)

4.4 Atherogenic dyslipidemia

Atherogenic dyslipidemia represents the combination of raised triglycerides (TG), low HDL-C, elevated apolipoprotein B (ApoB), small dense LDL and small HDL particles, and so on; all are independently atherogenic and are observed in type 2 DM and DMS. Low HDL-c is considered to be „a particularly key risk factor for CVD in both non-diabetic and diabetic individuals", „an independent contributor to CVD, in both men and women". Low HDL-c

and high TG levels are frequently found in insulin resistance, with or without type 2 diabetes, and both are risk factors for CVD (table 3) (Robins et al., 2003; Brunzell & Ayyobi, 2003).

5. Diagnosis of DMS

Although the present review does not have as purpose the detailed presentation of the way in which the diagnosis of DMS is made, we consider that few remarks are necessary in order to manage it correctly.

The literature of the past years regarding the management of this concept agrees upon the necessity of a team research, especially in the population of high risk, on national criteria, with subsequent establishment of a realistic management programme.

S Julius (and not only him) supports this point of view because "the clinical spectrum of the Metabolic Syndrome is variable and influenced by gender, ethnicity, and genetic susceptibility", especially in arterial hypertension, and even in borderline hypertension (Julius & Nesbitt, 1996). Paul Zimmet, from Australia, draws attention to the need of a "careful definition and management of the "tick test" in the DMS", which must rely on „evidence-based criteria"; he adds: "Tackling diabetes and obesity is likely to be the single most important challenge for Australia's public health in the 21st century. It is a battle that we can and must win!" (Eckel et al., 2005; Barr et al., 2006). More recently, a Joint Scientific Statement was necessary "in an attempt to unify criteria", to underline the fact that DMS is a "multifaceted, but distinct entity", and that "further progress depends in part on interdisciplinary dissemination of knowledge" (Table 6); moreover, "various diagnostic criteria have been proposed by different organizations over the past decade", which often led to confusion.

Simmons RK and collaborators evaluated the utility of metabolic syndrome from several points of view: pathophysiology, epidemiology, clinical work and public health, but also educational; the authors conclude that they agree with this „concept that focuses attention on complex multifactorial health problems", but they accept it only as „a diagnostic or management tool" with a limited practical utility (Simmons et al., 2010).

To gave up the widespread term of DMS that Sindrom metabolic, which is used for many years for this „cluster of risk factors", " is an unrealistic act, even impossible to fulfill, because the term is rooted in the medical literature"; DMS is: „a heterogeneous entity, composed of abnormal situations involved in the production of a metabolic imbalance with common metabolic links, but also with important differences in the etiopathogenesis of its components" (Balta, 2010).

Despite numerous criticisms of the concept by many authors, Kahn and collegues express „our recommendations to clinicians":

„All CVD risk factors should be individually and aggressively treated"

„Pharmacological therapy to reduce insulin resistance will be beneficial to patients with the metabolic syndrome"

„An aggressive research agenda to identify the underlying cause(s) of the CVD risk factor clustering"

…"it remains to be demonstrated that the impact of the syndrome exceeds that of the sum of its individual components" and so on (Kahn et al., 2005).

David Nathan (Massachusetts General Hospital, Boston) described the situation as "a firestorm about nothing" and adds about DMS:

- "it was raised from a research view",
- "it captured a confluence of clinical conditions that can occur together"
- "an important concept from an epidemiology view and to investigate whether these conditions had a single underling cause".

Hypertriglyceridaemic waist phenotype estimated prevalence: 20-25%
- Atherogenic metabolic triad (fasting hyperinsulinaemia, elevated apolipoprotein B levels and increased proportion of small LDL particles
- Elevated total cholesterol/HDL cholesterol ratio
- Postprandial hyperlipidaemia
– Fasting hyperinsulinaemia
– Glucose intolerance
– Increased risk of type 2 diabetes
– Increased cardiovascular risk

Table 6. Hypertriglyceridaemic waist phenotupe association with features of metabolic syndrome

We note some compelling conclusions regarding the current global state of DMS:

- "DMS is common and it has a rising prevalence worldwide.
- Now, DMS is both a public health and a clinical problem.
- The DMS is a complex of interrelated risk factors for CVD, DM.
- Three abnormal findings out of 5 would qualify a person for the metabolic syndrome.
- The term "metabolic syndrome" is acceptable for the condition of the presence of multiple metabolic risk factors for CVD and DM.
- The metabolic syndrome is not an absolute risk indicator.
- The metabolic risk factors are atherogenic dyslipidemia, elevated blood pressure, and elevated plasma glucose.
- The risk associated with a particular waist measurement will differ in different populations. We recommend the use of waist measurement as a useful screening tool in many primary populations"(Alberti et al., 2009).

Even if now we assign to DMS multiple metabolic risk factors and/or a complex of interrelated risk factors for CVD and DM, although we know that DMS substantially increases the risk of CHD, we do not know which of its defining characteristics (insulin resistance/ hyperinsulinaemia, small LDL particles, reduced adiponectin levels, increased CRP, etc.) are "critical therapeutic targets for the optimal management of CHD and type 2 diabetic risk" (Hu et al., 2001). We need to globally asses the individual risk of these patients

in order to optimally manage the dyslipidaemic state in this high-risk population. In the context of the current knowledge regarding the DMS, the patients diagnosed with arterial hypertension, DLP, or hyperglycemia will be actively investigated for DMS. We must insist upon the realisation of a complete diagnosis, specifying the risk score for CV and/or metabolic disorders that we found (table 5, 6).

Given the susceptibility to many other pathological conditions, we must use all clinical and paraclinical methods needed in order to establish a positive and differential diagnosis (ex. polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, some forms of cancer), especially if they are sugested by the familial genetic aspect, by the signs and simptoms and so on. The mesurement that are needed (weight, height, waist circumference or waist/hip ratio) for initial diagnosis of DMS and for follow-up will be taken in a proper manner, following the current guidelines (by gender, etnicity, etc.). It is estimated that the introduction of "waist circumference rather than the body mass index has been "a major conceptual leap", because it recognizes the much greater causal role of abdominal obesity than general obesity. (www.metabolicsyndromeinstitut/information /screeningdiagnosis/procedures-for-the-measurement-of-the-waist-circumference.php).

The canadian researchers Lemieux I, Pascot A, Couillard C et al., introduce a new notion, namely: „HYPERTRIGLYCERIDEMIC WAIST": a marker of the atherogenic metabolic triad: hyperinsulinemia, hyperapolipoprotein B, and small, dense LDL, in men. We note the depth of this interesting concept, its validation in a trial (Québec Health Survey) and its practical usefulness, at least from two points of view:

- first, the possibility of identifying men at high risk, with normal glucose levels or impaired fasting glucose state;
- secondly, because it avoids the exact procedure for measuring visceral fat by sophisticated and costly methods, such as magnetic resonance or computed tomography.

„The hypertriglyceridaemic waist phenotype significantly increased the odds of finding CAD in men, whereas impaired fasting glucose was not predictive of CAD in the absence of hypertriglyceridaemic waist":

- "the simultaneous measurement and interpretation of waist circumference and triglyceride level", "the hypertriglyceridaemic waist", may be a simple tool to identify individuals at high risk";
- "men characterised by the hypertriglyceridaemic waist phenotype had a substantially elevated total cholesterol/HDL-cholesterol ratio compared with those without this phenotype";
- results suggest that the hypertriglyceridaemic waist phenotype may be useful in the screening of patients with many features of DMS (Table 7), such as an elevated total cholesterol/HDL-cholesterol ratio, postprandial hyperlipidaemia, fasting hyperinsulinaemia and additional risk factors.

Identified by the simultaneous measurement of waist circumference and fasting triglyceride levels, this approach can be "a simple and inexpensive marker to better identify individuals at high risk of CVD and/or type-2 diabetes and to evaluate CHD risk in individuals with abdominal obesity"(Lemieux et al., 2002; Blackburn et al. 2003).

There are multiple laboratory tests and many of them are vital (glycaemic profile, lipids, inflammatory tests); we must not forget about exploring the thyroid function or investigating other systems (cerebrovascular, hepatic or renal). The new guidelines recognize the importance of elevated triglycerides and of reduced HDL cholesterol concentrations as useful lipid markers of the presence of an atherogenic "dysmetabolic" milieu. In DMS, the lipidic profile can vary, and so can the therapeutic options; they can be prescribed together with dietary changes or sustained physical effort.

Here are a few patterns:

- when there is a high LDL-cholesterol level, the use of statins as the drug of choice is preferred to reduce the risk of a first or recurrent CHD event;
- if we have a "normal" LDL-cholesterol level and typical dyslipidaemia, a fibrate is preferred as the first therapeutic option;
- if LDL-cholesterol and triglycerides are elevated, together with a relatively low HDL-cholesterol, patients are considered under "high risk" and combination therapy with both a statin and a fibrate is indicated, because of the high risk atherogenic profile - "atherogenic dyslipidemia" (Sacks, 2002).

Interventions which can improve insulin sensitivity, especially lifestyle modifications, weight loss, Mediterranean diet, and increased physical activity, remain the elements of choice in DMS, because of their favorable impact on DMS components. (Hu et al., 2001)

As an example for the complexity of what we call DMS, Zeller, Steg et al. insist that "fasting hyperglycaemia is the most important risk factor for development of severe heart failure in patients with metabolic syndrome"; these situations are associated with „a higher in-hospital case fatality rate"; strict control of glycemic levels in patients with DMS with or without a critical state is recommended by many authors and by the algorithm of the American Diabetes Association and the European Association for the Study of Diabetes (2006) (Zeller et al. 2005; Nathan et al., 2006).

Similarly, for a correct and complete diagnosis, Enzo Bonora et al. proposed a short list of novel (non-traditional) risk factors in order to emphasise the fact that, in the "metabolic syndrome approach", it is necessary to prove the "existence of underlying pathogenic disorders of the cluster, i.e. central obesity and insulin resistance"; to this end, the authors present a "systematization of biomarkers" that are useful in DMS and in clinical trials:

- chronic mild inflammation (e.g. C-reactive protein, CRP, white blood cells, WBC, erythrocyte sedimentation rate, ESR),
- increased oxidant stress (e.g. oxidized LDL, reactive exigent species, ROS),
- thrombophilia (e.g. fibrinogen, plasminogen activator inhibitor-1, PAI-1), - endothelial dysfunction (e.g. E-selectin, intercellular adhesion molecule-1, ICAM-1,
- vascular cell adhesion molecule-1, VCAM-1),
- adipose tissue derangement (e.g. adiponectin, leptin, resistin).

The authors consider that a better diagnosis and treatment of "several classic and ancillary components of the metabolic syndrome" will accomplish "a substantial reduction of the cardiovascular risk" (Bonora et al., 2003).

Matsuzawa Y, Funahashi T, and many others emphasize the importance of adiponectin; "one of these adipocytokines which we identified in human adipose tissue"; it circulates abundantly in human plasma, and has both anti-atherogenic and anti-diabetic effects. In addition, a series of clinical and experimental studies suggest that adiponectin may become a novel 'hot' marker of the Metabolic Syndrome (Matsuzawa et al., 2004).

Based on complicated lab research, Kumada M, Kihara S, Ouchi N et al. suggest the results above and conclude that „plasma adiponectin may become a novel biomarker for atherosclerotic vascular diseases, as well as plasma cholesterol and glucose levels" (Kumada et al., 2004).

The significance of adiponectin as „a negative risk for diabetes and its dual protective capacity", both against diabetes and atherosclerosis, makes the subject of much prestigious research; we are talking about „adipocytokines", considering the remark that "reduction of adiponectin may facilitate coronary plaque rupture" but, at the same time, adiponectin „suppresses both the atherosclerotic process and the production of an inflammatory cytokine," and so on.

Based on all these observations, it is obvious why „body weight reduction, physical exercise, and lifestyle changes" can raise plasma adiponectin levels. In addition, agents such as "thiazolidinediones, renin-angiotensin system blockers and glimepiride" have been reported to increase adiponectin concentrations (Weyer et al., 2001).

Wiecek et al. reported that plasma adiponectin levels are negatively correlated with mean blood pressure (BP) in patients with essential hypertension (Adamczak et al., 2003).

Some well known Japanese authors point out the association of obesity with increased risk for breast and endometrial cancers; also, high serum adiponectin levels are associated with an increased risk for breast cancer (Miyoshi et al., 2003).

Imaging tests are not routinely indicated, but they can be performed when previous examinations suggest cardiovascular complications.

Adverse clinical consequences and/or target organ damage appear during long term evolution of DMS; all these elements will be periodically investigated and quantified by specific methods. The most frequent example is represented by arterial hypertension, which evolves with very important target organ damage (left ventricular hypertrophy, progressive peripheral arterial disease, and renal dysfunction).

Using the NCEP/ATP III definition, Mulè et al. investigated the efect of SXM on markers of target organ damage, and they have demonstrated that these lesions can explain „the enhanced cardiovascular risk associated with the Metabolic Syndrome". The authors also conclude that there must be a global evaluation of the „influence of the SXM on some cardiac, renal, and retinal markers of target organ impairment" (Mulè et al., 2005).

We must not overlook the complications associated with DMS, representing short and long-term prognosis factors; there can be cardiovascular (coronary heart disease, atrial fibrillation, heart failure, aortic stenosis , ischemic stroke, and so on) or extra cardiac complications (nonalcoholic fatty liver disease, obstructive sleep apnea, breast cancer, cancer of the colon, gallbladder, kidney, prostate gland, and so on).

6. Management of DMS

Because DMS is associated with dramatically higher risk of DCV, diabetes, and so on, its recognition and follow-up have become a major issue in preventive cardiology.

According to the DMS concept and the recognition of its defining combinations (hypertriglyceridemia, hyperglycemia, hypertension, low HDL-C level, and greater waist circumference /adiposity) there are:

- a clinical method for identifying CVD risk and symptoms of an underlying disease or condition;
- the variation of cardiovascular and metabolic risk according to which syndrome components are present, their duration, and existing complications.

These elements represent the foundation of DMS complex management. (Ding et al., 2010).

6.1 Primary prevention

Primary prevention consists in a healthy life style, smoking cessation, caloric restriction, and a modified daily diet. A moderate increase of physical activity and a 7-10% weight loss over 6-12 months are also indicated.

Low caloric diet and moderate but sustained exertion are considered "the most important initial steps in treating metabolic syndrome" (Ford et al., 2002).

If we analyze each individual component of DMS reporting it to the DMS diagnosis, a greater chance of progression was observed, especially if we consider that hyperglycemia, hypertension, and low HDL-C level are the main risk factors; consequently, these risk factors represent a potential target for active and individual cardiovascular prevention in these patients (Després et al., 2008).

6.2 Secondary prevention

Secondary prevention is addressed to patients for whom lifestyle change is not enough and who are considered to be at high risk for CVD; these patients will receive medical treatment together with lifestyle changes.

All these will act "as a whole" on the basic mechanisms of DMS in order to reduce the evolutionary impact of all risk factors and all "metabolic and cardiovascular consequences", on short and long-term evolution.

Separate, incomplete or inconsistent approach of individual components of DMS is to be avoided; the emphasis will be laid on sustained reduction of individual risk, especially in patients with several DMS components and complications; only, in this way, we can really reduce „the overall impact on CVD and DM risk". (Lindström et al., 2003; Tuomilehto et al. 2001).

After the complete diagnosis is established, the management of DMS must be more comprehensive and more aggressive compared to other clinical situations, in order to reduce the risk for CVD and DM; thereby, a complete evaluation of cardiovascular risk according to present guidelines of medical practice is of outmost importance.

Framingham risk scoring (or other risk scores, although they include different components) will be used to estimate „10-year atherosclerotic disease risk" and may guide the use of medication therapy (Spellman & Chemitiganti, 2010; Nicholls et al., 2007).

6.3 Medical care

The initial management of metabolic syndrome involves lifestyle modifications (changes in diet and exercise habits).

The choice of drug and dose should be individualized to the patient and titrated to achieve guideline-recommended goals.

Diets that promote the consumption of fruits, vegetables, and low-fat dairy products ("DASH-style diet") help lower blood pressure and may lower risk of stroke. The consumption of products with high-glycemic-index will be avoided.

Increasing physical activity is associated with a reduction in the risk of stroke, at least 30 minutes of moderate intensity activity on a daily basis, maintaining long-term adherence.

Weight reduction among overweight and obese persons is recommended to reduce blood pressure and risk of stroke.

Bianchi C et al. stipulates the basics of food diet for prevention and treatment of DMS:

- protein for 10-20% of total daily energy;
- saturated fatty acids and trans-unsaturated fatty acids ≤ 10% of total energy, and further lowered to < 8%, if serum LDL-cholesterol level is increased;
- cholesterol intake: 300 mg or less per day;
- carbohydrates: 45-60% of total energy, vegetables, legumes, fruits, and whole-grain cereals: the most appropriate sources of carbohydrates;
- foods rich in dietary fiber: ≥ 40 g/d (or 20 g/1000 kcal/d), about half in soluble form;
- sodium restriction can reduce systolic blood pressure in hypertensive patients;
- 30 minutes of walking a day: all overweight subjects;
- pharmacotherapy may be necessary for cardiovascular risk factors: LDL-cholesterol, hypertension, T2DM, and obesity (Bianchi et al., 2006).

The medical care is represented by "a multi-drug treatment", in order to reduce morbidity and prevent DMS complications; the treatment must be with metabolic and glucidic neutrality, with respect to the accompanying disturbances of the DMS":

- angiotensin converting enzyme inhibitors (ACEI) or/and angiotensin-II-receptor blockers;
- anti-diabetic treatments to improve glycemic control, with metformin and thiazolidinediones, representing "a rational first-line treatment of patients with type 2 diabetes mellitus ";
- obesity and visceral obesity can respond to certain drugs with "the potential possibility of ameliorating the metabolic aspects in obese patients": Sibutramine, Orlistat and Rimonabant (the first inhibitor of CB1 receptors);
- although a therapeutic class of drugs capable of reducing the "inflammatory state" from DMS has not been established, there are many classes of drugs indicated in these patients (statins, fibrates, ACEIs, and thiazolidinediones), with an anti-inflammatory action;

- the procoagulative state in these patients, associated with elevation of the circulating levels of fibrinogen, factor VII, PAI-1, together with an increased platelet aggregation, determine the introduction of low-dose aspirin, with or without other anti-inflammatory agents (Antithrombotic Trialists' Collaboration, 2002).

In dyslipidemia, primary aims for therapy are:

1. lower TG (as well as lowering ApoB and non-HDL cholesterol),
2. raise HDL-c levels,
3. reduce LDL-c levels (elevated levels represent a high risk in the metabolic syndrome).

Fibrates (PPAR alpha agonists) improve all components of atherogenic dyslipidaemia (elevated triglyceride and low HDL-C levels), especially in overweight patients, and reduce the risk for cardiovascular disease in DMS,

For patients with elevated triglyceride levels, the addition of omega-3 fatty acids is likely to produce added benefit (according to clinical trials).

Statins are administered in order to reduce all apoB-containing lipoproteins and to achieve ATP III goals for LDL-cholesterol, as well as for non-HDL-Cholesterol; the multiple benefits are confirmed through many clinical trials „at all indicated ranges", the pleiotropic and metabolic effects being an "undisputed reality".

Management of reduced high-density lipoprotein cholesterol (HDL-C) remains controversial, not yet having a specific treatment; some measures have proved a positive influence: dietary changes, sustained physical efort, some statins (ex. Rosuvatatin), etc.

The latest guidelines insist on LDL-cholesterol being „the primary target of treatment by adequate use of statins"; although high levels of LDL-cholesterol are not necessarily associated with DMS, they will be properly quantified and treated, for reducing the cardiovascular risk.

Fibric-acid derivatives, bile acid sequestrants, and ezetimibe may be useful in patients who have not achieved target LDL with statin therapy or cannot tolerate statins (Eckel et al., 2005; Alberti et al., 2009; Robins et al., 2003; Heart Protection Study Collaborative Group, 2003; The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society 2011).

Hypertension remains a clinical target according to present guidelines; regular blood pressure screening, lifestyle modification, and drug therapy are recommended. The focus must be on clinical situations associated with target organ damage, diabetes, or renal complications. Hypertension and diabetes, both components of metabolic syndrome, are known to be associated with renal dysfunction; oxidative stress and inflammation mediated by renin-angiotensin system activation are the most frequently involved mechanisms. Other mechanisms acting singly or in combination, linking obesity to chronic kidney disease, have been proposed: renal adaptation to increased body mass, with an increased excretory load, sodium retention, insulin resistance, renal lipotoxicity, etc. (Praga, 2002).

Microalbuminuria, however, was more common in subjects who had a constellation of all 3 components of metabolic syndrome than in those without. Presently, microalbuminuria is an early marker of renal dysfunction due to hypertension, predicts the onset of kidney

disease in diabetic and nondiabetic subjects, and reflects widespread endothelial dysfunction, microvascular damage, and possibly inflammation. (Gerstein et al., 2001; Festa et al., 2000). The precise pathogenetic basis of microalbuminuria in metabolic syndrome is not known; it is, however, possible that microalbuminuria in metabolic syndrome reflects renin-angiotensin system activation and resultant oxidant stress, inflammation, and endothelial injury.

Dzau VJ, Safar ME, amongst many other elite scientists, have shown that hypertension, dyslipidemia, and insulin resistance are associated with renin-angiotensin system activation and generation of large amounts of angiotensin II (Dzau & Safar, 1988; Shinozaki et al., 2004).

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are useful antihypertensive drugs; some clinical trials suggest that they have advantages over other drugs, in patients with diabetes, and that 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" (Chobanian et al., 2003).

Diabetes mellitus, recognized as „a true cardiovascular disease", raises particular problems of follow-up and treatment; the periodic screening with the assessment of end-organ complications is required even from the beginning of its evolution;

- the sustained control of blood pressure and dyslipidemia, along with diet, regular physical exercise, and the maintaining of normal body weight is recommended;
- as in hypertension, for DM, medical practice guidelines come with many details for each of „these pursue matters" (ex. JNC 7, update 2009).

Medical treatment of hyperglycemia in DMS begins with an insulin-sensitizing agent (ex. metformin), which proved that it can reverse the complications DMS, especially together with fibrates and thiazolidinediones.

Multiple research have shown the possibility that drugs that reduce insulin resistance will delay the onset of type 2 diabetes and will reduce CVD risk, when DMS is present (ex. „Diabetes Prevention Program" (DPP) with metformin, thiazolidinedione in delaying or preventing type 2 diabetes in impaired glucose tolerance (IGT) and insulin resistance) (www.idf.org).

Of course, we should not avoid prescribing aspirin for its well-deserved preventive actions, especially in patients with a high CV risk given by DMS, unless contraindicated.

Many other recommendations are necessary:

- patients with diabetes should be referred to a diabetic nutritionist, if not an endocrinologist;
- patients with high CV risk should be referred to a cardiologist for primary or secondary prevention of CVD;
- patients who are at high risk for obesity-associated morbidity and mortality with BMI greater than 40 kg/m2 or with BMI >35 kg/m2 plus one or more significant co-morbid conditions may be referred for consideration of bariatric surgery, when less invasive methods of weight loss have failed, etc., for more than 5 years;
- liposuction is used for cosmetic weight loss, but evidence shows that liposuction of abdominal subcutaneous fat (with no removal of visceral fat) has little effect on cardiometabolic risk parameters.

Moreover, it is required to follow up the effect/effects of the prescribed treatment, especially in cases of hypertension, DLP and DM, with a periodic assessment of patient adherence to treatment; attention will be directed to prescribe optimal combination regimens, respectively those recognized in reducing the CV risk.

Of course that the management of DMS is impossible to be wholly presented; it is a subject of great practical interest, but its defining elements are found in specialized literature and guides.

7. Conclusions

With all these questions, different opinions and debates, "the metabolic syndrome serves as a call to action for practitioners to focus more carefully on risk prevention above and beyond traditional …". (Smith, 2006).

Jean Pierre Després (Institut Universitaire de Cardiologie et de Pneumologie de Québec) presents the DMS as "a work in progress" and adds :« I think it should be redefined as a constellation of metabolic abnormalities associated with visceral fat and insulin resistance; this would simply things and clarify a lot of confusion over this." (Després, 2008)

DMS was and remains an attractive subject in many ways, theoretical and practical, as demonstrated by all of the research so far; it remains a concept with great practical use, a heterogeneous entity based on a metabolic imbalance that has not yet found the best definition, the optimal nosological framing, widely accepted, even if it will reach soon 100 years of existence.

We propose the terminology of CARDIOVASCULAR DISMETABOLIC SYNDROME (CV DMS) which express a metabolic disorder, multifactorial entity that require the participation of several medical specialties (even over 10 specialities) in order to quantify and consolidate the defining elements of cardiometabolic risk and defining appropriate management in real time.

In order to reduce the confusion in the medical community, universal agreement on the definition and clinical tools to assess the DMS would be very helpful and eforts for additional international consensus activities have been made; all this research will determine all the "preventive and screening strategies for the dismetabolic syndrome".

Theoreticians and practitioners, laboratory doctors, lipidologists, diabetologists, nutritionists, or hypertensiologists, cardiologists, nephrologists, neurologists, endocrinologists, but also pediatricians, geneticists, family doctors and so on all participate in this complex process, because only teamwork can, indeed, to define actively, to monitor and improve multiple abnormal components of this entity called CARDIOVASCULAR DISMETABOLIC SYNDROME (CV DMS).

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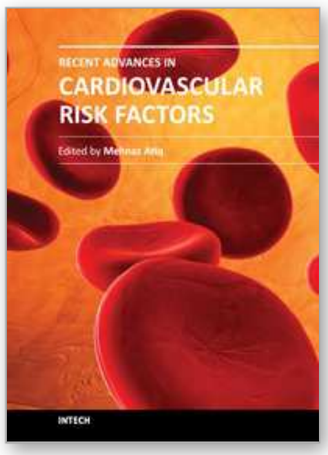

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Among the non-communicable diseases, cardiovascular disorders are the leading cause of morbidity and mortality in both the developed and the developing countries. The spectrum of risk factors is wide and their understanding is imperative to prevent the first and recurrent episodes of myocardial infarction, stroke or peripheral vascular disease which may prove fatal or disabling. This book has tried to present an update on risk factors incorporating new research which has thrown more light on the existing knowledge. It has also tried to highlight regional diversity addressing such issues. It will hopefully be resourceful to the cardiologists, general practitioners, family physicians, researchers, graduate students committed to cardiovascular risk prevention.

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