THE DYSMETABOLIC SYNDROME – DEFINITION, HISTORY, COMPONENTS

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Abstract

Some researchers tend to think of the dysmetabolic syndrome as being the most important medical problem of the 21st century beginning.

The dysmetabolic syndrome is rather difficult to estimate because of the numerous existing points of view regarding the elements needed for the diagnosis.

It isn't about a singular disease, but an association of impairments that can appear simultaneously or gradually in the same individual, caused by associating the genetic and environmental factors (+ lifestyle) with the insulin - resistance, considered as the fundamental pathogenic component.

The first definition of the metabolic syndrome (MS) was formulated in 1998 by a group of researchers from OMS (the group being concerned with studying diabetes). It made precise the fact that the syndrome is defined by the presence of type II diabetes mellitus or the altered tolerance to glucose combined with at least 2 other factors (hypertension, increased level of blood lipids, obesity and microalbuminuria).

Starting with that first definition (initial one) of the metabolic syndrome a range of alternative definitions was suggested. The most widely accepted definition was formulated by EGIR (European Group for the Study of Insulin Resistance) and NCEP (USA National Cholesterol Education Panel).

Introduction

Such a great interest taken in this theme starts from the increased prevalence of the metabolic syndrome and its association with a decreasing hope for a longer lifespan, especially by the increasing of the cardiovascular mortality, the increasing of diabetes, myocardial infarction and cerebrovascular disease risk.

Some researchers tend to think of the dysmetabolic syndrome as being the most important medical problem of the 21st century beginning. Recent studies showed the epidemic proportions that this affection reached worldwide (global numbers show a prevalence of 20 - 25%). The diagnosis, clinical evaluation and efficient treatment of such a big number of patients are heavily trying the public health systems. On the other side, the delaying in curing the dysmetabolic syndrome leads to an increasing of the cardiovascular diseases and type II diabetes incidence, with disastrous consequences over the human society. It is estimated that, in 2020, approximately 2/3 of the world morbidity will be due to the non - transmissible confirmed diseases. Passing to a

food that is rich in refined products, food of animal origin and fats plays an important part in the worldwide epidemics of obesity, diabetes mellitus and cardiovascular diseases (non – transmissible confirmed diseases). Unfortunately, the obesity generating media, amplified by the number of cultural modifications associated with globalization, make it increasingly difficult to adopt a healthy lifestyle, especially among children and teenagers (1).

The dysmetabolic syndrome is rather difficult to estimate because of the numerous existing points of view regarding the elements needed for the diagnosis. It isn't about a singular disease, but an association of impairments that can appear simultaneously or gradually in the same individual, caused by associating the genetic and environmental factors (+ lifestyle) with the insulin - resistance, considered as the fundamental pathogenic component. The modern lifestyle, which is stressful, always in a rush after success and fortune, associates the hyperglucid/hyperlipid food with the sedentariness promoted by the comfort of the contemporary civilization.

Definition

According to the encyclopedic dictionary of the Romanian language the term **"syndrome"** = group of signs and symptoms that appear together during a pathological process, giving it the characteristic note.

The dysmetabolic syndrome expresses a complex disturbance of the genetic metabolism of the organism, including disturbances of the lipid metabolism (obesity, dyslipidemia), the carbohydrate metabolism (altered tolerance to glucose/ type 2 diabetes mellitus), the protein metabolism (hyperuricemia), as well as the arterial hypertension (a hemodynamic disturbance having a metabolic starting point) (2).

Terminology

The term **"syndrome"** derives from the Greek word *sundromos* (sun-syn + dromos= a fugi) and it means *"to run together"*.

The dysmetabolic syndrome was diversely named in time: the plurimetabolic syndrome, the X syndrome, the X plus syndrome, the X metabolic syndrome, the cardiovascular metabolic syndrome, the insulin - resistance – dislipidemia syndrome, the atherogenic metabolic syndrome, the syndrome of atherogenic factors' agglomeration, the deadly quartet). Recently, there was used the MetS acronym as replacing the term of Metabolic Syndrome.

Out of the numerous terms suggested to define this nosologic entity, the World Health Organization (OMS) –(WHO), the International Diabetes Federation (IDF) and other international bodies agreed upon the term **"metabolic syndrome".** Nevertheless, from a semantical point of view, this term is not correct; let's not forget that the metabolism *per se* represents a natural phenomenon. Thus, if we refer to its dysfunction, it would be logical to call it "**dysmetabolic"** (ex.: we call the disturbance of the lipid metabolism "dyslipidemia", not "lipidemia").

History

As early as 250 years ago, long before the MS description, the Italian physician and anatomist Morgagni identified the association between visceral obesity, HTA (arterial hypertension), atherosclerosis, the high levels of uric acid in the blood and the frequent respiratory disorders during sleep (the obstructive apnea) (4).

In 1920, Nicolae Paulescu, speaking about obesity and diabetes, said that "most frequently, the obese people become glycosuric, as if the two affections (obesity and fat diabetes) represent two consequent phases of the same pathological process" (5).

In 1927, Maranon, the founder of modern endocrinology in Spain, explicitly described the fact that the arterial hypertension is a pre - diabetical stage and this concept is similarly applied to obesity. Maranon also underlined the fact that food is essential for preventing and treating these disturbances (4).

At the middle of the 20th century (1947), Vague, a French physician, was the first to identify android obesity (adiposity of the superior part of the body) as being the condition the most frequently associated with diabetes mellitus (Dz) and cardiovascular diseases.

The often simultaneous presence of obesity, the high level of blood lipids, diabetes mellitus and HTA (arterial hypertension) was first mentioned under the name of plurimetabolical syndrome in the 60's.

In the 70's, Moga, Orha, Haragus (6,7) from Cluj supported the idea of the existence of a close connection among the components that constitute the dysmetabolic syndrome at present, correlating them to the cardiovascular diseases. From the point of view of the school from Cluj, the atherosclerosis is represented by a complex disturbance of the metabolism, vaso – motility, coagulation, hydro - electrolytic and mineral equilibrium (8).

The cardiologists were the first to notice the connection between the major disturbances of the dysmetabolic syndrome. Making an inventory of the risk factors for the coronary diseases, alongside with HTA they recorded dyslipidemia (hypercholesterolemia/hypertri-glyceridaemi) obesity, diabetes and hyperuri-caemia, as well as food factors, the sedentary lifestyle, environment factors, psychosocial factors, etc.

Towards the end of the 80's, the assembly of glucose, insulin metabolism disorders, obesity, dyslipidemia and HTA received the mysterious name of "X syndrome". In 1988, Reaven G., an endocrinologist physician from Stanford University, was the one who took a big stride forwards, interpreting the association of diabetes, obesity, dyslipidemia and arterial hypertension by their pathogenic relationship with the peripheral insulin - resistance. He named this association "X syndrome", the name underlining the doubtfulness that accompanied the emitting of the apparently new concept (9). The insulin resistance and the compensatory hyperinsulinism were associated with each component of the dysmetabolic syndrome, offering thus a physio -pathological connection between them. Continuing this logical chain, one can naturally reach the conclusion that the dysmetabolical syndrome represents a complex disturbance of the energetic metabolism, in close connection with the insulin secretion altering, influenced

in its turn by the sensitivity/resistance to insulin (2).

Ferranini and collab. resumed this idea, confirming that this assembly of disturbances is provoked by the insulin – resistance and, after several years, they called it the "insulin – resistance syndrome" (4).

Afterwards, it was found out that the spectrum of metabolic disturbances is larger. Zimmet and Serjentson (10) speak about the "plus X syndrome" signaling the association with hyperuricaemia, sedentariness and old age. The X syndrome generates high degrees of free radicals, which are harmful to the cell, causing a premature aging. Vladimir Dilman, coauthor to the paper "The Neuroendocrine Theory of Aging" refers to the insulin – resistance as being a pathology connected to age. The blood glucose level tends to increase with age, accelerating aging by connection to proteins (11). During mid 70's, the biologist Anthony Cerami discovered the fact that the chronically increased glucose levels represent the main trigger in the chemical process of manufacturing the final glycolsylation products (AGE = Advanced Glycosylation End). AGE are involved in the processes of normal and accelerated aging, by chemical reactions between glucose and molecular proteins, producing serious damages at the level of cellular membranes and collagen fibers (12).

The appearance of the metabolic syndrome notion was due to the fact that, more often than not, the risk factors associate for the same individual. This suggests that, on the one side, there is possible a common etiopathogeny, and, on the other side, it was considered that it offers a better capacity to predict risks and, therefore, to intervene.

In 1998, the first definition of the metabolic syndrome (MS) was formulated by a group of researchers from OMS (the group being concerned with studying diabetes) One year later, the OMS definition was accompanied by a criteria list meant to the clinical diagnosis. It made precise the fact that the syndrome is defined by the presence of type II diabetes mellitus or the altered tolerance to glucose combined with at least 2 other factors (HTA, increased level of blood lipids, obesity and microalbuminuria).

The term **dysmetabolic syndrome** corresponds better to the biochemical reality. It is envisaged an increase of the biochemical disturbance number that can be identified.

Data about the dysmetabolic syndrome prevalence

Current estimations show that, in the USA, almost 1 out of 4 adults have, at present, the dysmetabolic syndrome (MS) and the prevalence is increasing (13); even more alarming are the reports that show an ever-increasing number of obese children who are going to advance MS until they are 20 (14).

The most documented data about the prevalence of the dysmetabolic syndrome are the ones coming from NHANES III (National Health And Nutrition Examination Survey III, USA) (13). According to these data, in the USA, the prevalence of the dysmetabolic syndrome is 23 – 24%, but with higher variations of this percentage depending on age, ethnical group or race. Thus, the prevalence of MS is <10% between 20-29 years of age, 20% between 40-49 years of age and 45% between 60 – 69; the higher prevalence was recorded for the Americans of

Hispanic origin/Mexicans (32%), for Afro – Americans being 22%, and for the white population (Caucasian) being 24%.

Other studies, also from the USA, report incidences of 55.2% for the Amerindians (of ages ranging between 45 – 75 years) (15), 17% for the American Arabs (of ages ranging between 20 -75 years) (16) or 13.1% for the Inuits (17).

More recent observations show that these percentages are increasing, especially for the 3rd age group (18). Probably, this increase is also due to the fact that obesity is more frequent with the 3rd age subjects. It is sad that the "epidemic" of obesity will continue to determine an increase of MS prevalence.

The researches demonstrate the fact that obesity is obviously associated with MS, especially in children and young adults. Weiss and collaborators (14) found out that MS prevalence is 0% in children and teenagers of a normal weight and in overweight ones, but it increases to 39% in the moderately obese ones, reaching up to 50% in the severely obese ones.

The data that are comparable for the prevalence of the syndrome in Europe indicate its presence in almost 30% of the population aging over 50. The European Group for the Study of Insulin – Resistance (EGIR), by analyzing 8 European studies, found a frequency of the dysmetabolic syndrome in non - diabetic subjects of ages ranging between 40 – 55 years old (according to the OMS criteria of defining the syndrome) as being between 7% and 36% for men and 5% and 22% for women (the MS prevalence is of 14% in Finland, 23% in Ireland, 25% in Scotland, <10% in France). The big variation in the incidence of the dysmetabolic system in Europe is due to the different study methodology, the different structure of the studied populations and, especially, to the adopted diagnosis criteria.

We don't have exact data for the prevalence of the dysmetabolic syndrome in the population of Romania. Preliminary data from the Urziceni Study (19) showed a prevalence of about 23% in adults.

Risk factors

The main risk factors associated with the dysmetabolic syndrome are:

- Abdominal obesity,
- Arterial hypertension (HTA)
- Low levels of HDL – cholesterol ("good" cholesterol)
- Low levels of blood triglycerides

Other factors that may favor the developing of the dysmetabolic syndrome are:

- Cardiovascular diseases
- Polycystic ovary syndrome
- Nonalcoholic fat liver
- Alcanthosis nigricans
- Non - Caucasian ethnic (obesity and CV diseases are more frequent in persons of African origin rather than in the populations of Caucasian origin)
- Sedentary lifestyle
- Age >40years (the hormonal variations at menopause, for example, are associated with an increase of the total adiposity and a fat distribution at abdominal level and, therefore, a higher risk for the metabolic syndrome developing)
- Gestational diabetes history or intolerance to glucose

- Familial history of type 2 diabetes mellitus, arterial hypertension, cardiovascular diseases

At present, there are known numerous other cardiovascular risk factors (pro - inflammatory status, pro-thrombosis status, micro – albuminuria, etc), their number being on the increase and bringing into discussion the metabolic syndrome itself.

The presence of the dysmetabolic syndrome confers a three times higher risk of appearance for the coronary disease and the cerebral vascular accident, doubling mortality on these accounts. If diabetes mellitus isn't already present, the dysmetabolic syndrome increases the risk of type 2 diabetes mellitus appearance by 5 times.

In addition to the risk of cardiovascular diseases and diabetes mellitus, the metabolic syndrome was associated with an increased incidence of cancer, being supposed to be induced by the excess of insulin in the blood circulation, a consequence of the resistance to insulin (20). The Canadian researchers studied the connection between the resistance to insulin, excess of insulin in the blood stream and cancer. Obesity contributes with 14 – 20% deaths owing to cancer, both in women and in men, with a risk increase especially for the colon and rectum, stomach, pancreas and liver cancer in men, and ovary, non – Hodgkin lymphomas, breast, uterus and liver cancer in women (21).

Not all overweight individuals develop the metabolic syndrome; it is supposed that a genetic factor is involved. The genetic susceptibility and the lifestyle are known to play a role in being insulin - sensitive to insulin. It seems that the genetic factors are at the basis of 50% of the sensibility - to - insulin cases, while obesity and the lack of physical activity each represent 25% of the causes (21).

Stress can also play a part in the metabolic syndrome. Researches showed that the increase of the cortisol levels, probably caused by the daily stress in the individuals having a genetic susceptibility, may lead to the metabolic syndrome developing by the increase of the abdominal obesity (and of the number of persons having the metabolic syndrome) among the subjects who are at a low social – economic level as against those at a high social – economic level (23). The data come from a male subgroup belonging to the same specimen category showed modifications in the levels of cortisol and epinephrine (adrenaline), which suggest an increased actuation by stress in those with metabolic syndrome as compared to those who showed no signs of MS (24). The increased cortisol levels, especially when they are accompanied by emotional stress, lead to a bigger accumulation of fat at the level of the abdominal adipose tissue that contains an increased number of receivers for cortisol (25).

Despite the numberless publications dedicated to this subject, the primary cause of the energetic metabolism disturbances, as well as the genesis of the various disturbances that make up the picture of the dysmetabolic syndrome are not known yet.

The components of the dysmetabolic syndrome

There are numerous points of view as regards the elements needed for diagnosing the dysmetabolic syndrome. Also, there are differences of opinion as concerns the limits

from which a parameter can be considered as being a pathological one.

Starting with the first definition (initial one) of the metabolic syndrome done by an OMS working group (in 1998), a range of alternative definitions was suggested. The most widely accepted definition was formulated by EGIR (European Group for the Study of Insulin Resistance) and NCEP (USA National Cholesterol Education Panel). Nevertheless, OMS and EGIR definition is limited as concerns the clinical applicability and acceptance. NCEP introduced the ATP III definition (Adult Treatment Panel III) that had more success owing to its simplicity.

The definition of the dysmetabolic syndrome according to **OMS** (The World Health Organization) (26)

- Diabetes mellitus/IFG/IGT/insulin resistance (evaluated by the euglycemic clamp method) and at least 2 of the following parameters:
- BMI>30 kg/m^2 or the waist/hip ratio> 0.90 in men
  >0.85 in women
- TG serous ≥ 150 mg/dl (>1.7 mmol/l) or
  HDL - cholesterol < 35 mg/dl (<0.9 mmol/l) in men 39 mg/dl (< 1.0 mmol/l) in women
- The rate of excretion of the urine albumin > 20 μg/min or albumin/creatinine ratio≥30 mg/g
- Blood presure ≥ 140/90 mmHg

IFG (Impaired Fasting Glucose) = (basal) à jeun glycemia modified/affected (110 – 125 mg/dl) (OMS classification 1998). Increased à jeun glycemia values that are over the normal level, but without reaching diagnosis values for the diabetes mellitus; at 2 h after administering 75 g of glucose per os, the glycemia level is normal.

IGT (Impaired Glucose Tolerance) = tolerance altered to glucose (glycemia at 2 h after oral loading with 75 g of glucose 140 – 199 mg/dl) (OMS classification 1980, 1985). Non - diabetic values of the à jeun glycemia (from normal values to increased ones, but <126 mg/dl of the venous plasma) and increased glycemia values of over the normal level at 2 h after the oral administrating of 75 g of glucose (between 140 and 199 mg/dl), without reaching, though, the values that characterize the diabetes mellitus.

During the last years, IGT and IFG were reunited under the term of **prediabetes.**

The method of the hyperinsulinemic/euglycemic clamp represents a truthful indicator of the sensibility/resistance to insulin. This is determined during a continuous perfusion of a solution that contains insulin in a concentration that allows the keeping of insulinemia constant at a value of 50, 75 or 100μU/ml. This increased concentration is accomplished in order to ensure an as high as possible occupying of the insulin receivers from the peripheral tissues. Normally, the maintaining of this insulinemia would rapidly lead to hypoglycemia. Its avoiding, in parallel with the insulin administrating, is done by introducing i.v., with the help of a pump of controllable capacity (delivery rate), a glucose quantity (variable) that is necessary to keep glycemia within normal and constant values. The quantities of glucose administered for preserving euglycemia indirectly reflect the

sensibility to insulin; the higher the glucose need is, the better the tissue insulin - sensibility. The lower the insulin need is (owing to the low peripheral using), the higher the insulin resistance.

EGIR definition (European Group for the Study of Insulin resistance) (27)

- Insulin - resistance or hyperinsulinemia à jeun >25% and, at least, 2 of the following parameters:
  - Plasm glucose à jeun ≥ 6.1 mmol (excluding diabetes)
  - Blood presure ≥ 140/90 mmHg or treatment for HTA
  - TG ≥ 2 mmol/l or HDL cholesterol < 1 mmol/l or treatment for dyslipidemia
  - Waist circumference ≥ 94 cm for men and ≥ 80 for women

The definition of the dysmetabolic syndrome according to **NCEP ATP III** (the USA Cholesterol Education Panel, Adult Treatment Panel III) (28,29)

At least 3 of the following parameters:

- Waist circumference > 102 cm with men, >88 cm with women
- Serous triglycerides ≥ 150 mg/dl (>1.7 mmol/l)
- HDL cholesterol < 40 mg/dl (1.0 mmol/l) with men, < 50 mg/dl (1.3 mmol/l) with women
- Blood presure ≥ 130/85 mmHg
- Serous glucose ≥ 110 mg/dl (> 6.1 mmol/l)

Other definitions of the dysmetabolic syndrome were suggested, complicating the possibility of an accepted international definition.

AACE definition (American College of Endocrinology) (30)

The presence of at least 1 factor out of the following:

- Diagnosis of CV, HTA, polycystic ovary syndrome, nonalcoholic fat liver or acanthosis nigricans disease
- Family history of type II diabetes mellitus, HTA or CV diseases
- Gestational diabetes history or intolerance to glucose
- Non - Caucasian ethnic
- Sedentariness
- BMI > 25 kg/m^2 and/or waist circumference > 102 cm with men and > 88 cm with women
- Age > 40 years

And at least 2 out of the following parameters:

- ✓ Serous TG ≥ 150 mg/dl
- ✓ HDL cholesterol < 40 mg/dl with men, < 50 mg/dl with women
- ✓ Blood presure ≥ 130/85 mmHg

À jeun glucose 110 – 125 mg/dl or at 2 h post – prandial 140 – 200 mg/dl (diabetes is excluded from the AACE definition.

The parameters of defining the dysmetabolic syndrome, as employed by the "N.C.Paulescu" Institute (2):

The syndrome composition	The defining parameter and level

Abdominal obesity	Abdominal circumference > 102 cm with men and > 88 cm with women
Plasmatic triglycerides	≥ 150 mg/dl
HDL – Cholesterol	< 40 mg/dl with women and < 50 mg/dl with men
À jeun plasmatic glucose	≥ 110 mg/dl (ADA recommends > 100 mg/dl)
Plasmatic uric acid	≥ 7 mg/dl with men and ≥ 5.7 mg/dl with women
Arterial pressure	≥ 130/85 mmHg

ADA = American Diabetes Association

There isn't any view unity as regards the parameters that define the dysmetabolic syndrome, the various bodies of an international renown in the field having own exigencies in their nominalization, a fact that can be corrected by a constructive dialogue based on scientific data.

The lack of a minimal consensus regarding the basic elements of the dysmetabolic syndrome expresses the different levels of thoroughgoing into and interpreting of the syndrome by the researchers in the domain; we exclude the priority subjectivisms and the hierarchic differentiation vainglory of the organizations.

Recently, the controversies on the MS intensified themselves. An all - inclusive (and official) analysis regarding the metabolic syndrome was published by Kahn and collaborators (31). The authors present a series of criticisms concerning the definition and the physio -pathological basis of the MS:

I. Some of the criteria used for defining MS are ambiguous or incomplete. For example, it is not clear if the definition of the blood pressure refers to values of the systolic pressure that has to be > 130 mmHg or of the diastolic pressure > 85 mm Hg, or if both conditions have to be fulfilled; also, there isn't either specified the way blood pressure should be measured (in clino or ortho static – postural - position). Such ambiguities affect the sensibility and specificity of the diagnosis and, undoubtedly, led certain physicians to wrong diagnoses (+).
II. It is clear that the definition of the syndrome differs in the listed criteria. For example, micro - albuminuria appears in the OMS definition, but not in the ATP III one; the insulin – resistance is relevant for the OMS definition, but not for the NCEP ATP III one. Until at present, there has been published no survey of the clinical records in favor of including or excluding any criterion for any of the 2 definitions (OMS and NCEP ATP III).
III. Certain criteria (for example the waist circumference, HDL – cholesterol) differ by gender, implying the fact that the relationship between the risk factor level and the results differs as depending on gender; there was found no proof that could justify the establishing of certain guide marks by taking into account one's gender (used as criteria the way those connected to CV diseases are). Foe example, it is not known if the same mass of adipose intra - abdominal tissue carries various risks in men as compared to women. An analogous reason can be put forth as concerns the variation of these

criteria depending on race and ethnic group.

IV. Finally, the reason supporting the criteria is that the syndrome components are associated with the insulin – resistance (26, 28), but one could notice the fact that not all the subjects with the dysmetabolic syndrome are insulin – resistant. Recently, the ATP III definition went through reviewing, enlarging the MS etiological basis from the "insulin – resistance" taken singularly, to "obesity and disturbances of the adipose tissue", as a "constellation of independent factors" that indicates specific MS components (31). The studies also illustrate another deficiency of the present dwelling upon the MS diagnosis. Both the OMS definition and the ATP III one weigh each risk component equally; still, it is obvious that certain risk factors that are included into the definition have a bigger predictive importance than others. It is extremely important to know from a list of all the cardiovascular risk factors (known ones) the hierarchy of the combination having the highest predictive value.

Briefly, the conclusions reached by Kahn and collaborators pursuant to the carried out analysis are the following:

1) The criteria are ambiguous or incomplete. The motivation for thresholds (limit values) is badly defined.

2) The insulin – resistance as a unique etiology is unsure.

3) There is no clear basis for including or excluding other risk CV factors.

4) The value of the cardiovascular risk is varying and depending on the specific risk factor presence.

5) The CV disease risk, associated with the syndrome, doesn't seem to be higher than the sum of its component parts.

One of the initial purposes of the MS, the amelioration of the CV disease risk prediction, proved to be a disappointing one. There are needed subsequent studies that should ascertain if modifying the actual MS definition, with adding the risk parameters for the CV disease, can optimize its predictive value. The second purpose of the syndrome, namely identifying a group of CV disease risk factors that confer a higher risk when analyzed together, proves an unrealistic one at present.(33).

The International Diabetes Federation (IDF) recorded an important achievement in MS physiopathology and diagnosis, suggesting that the key element is the *central obesity* (34). All the MS components, suggested by all the actual definitions are to be found in the clinical and biological survey of the central obesity (abdominal one) (35).

The **FID** definition (the International Diabetes Federation)(34)

1) The central obesity (defined by the waist circumference ≥ 94 cm with the European men and ≥ 80 cm with the European women, with characteristics values for various ethnic groups) and ≥ 2 of the following parameters:
2) Low level of the TG ≥ 1.7 mmol/l (150 mg/dl) or a cure that is specific for hyperlipidemia.
3) Low level of the HDL – cholesterol <1.03 mmol/l (40 mg/dl) with men and
   < 1.29 mmol/l (50 mg/dl) with women or specific cure for dyslipidemia.

4) HTA, systolic blood presure ≥ 130 mmHg or dyastolic blood presure ≥ 85 mmHg or cure for hypertension that was previously diagnosed.
5) The increased levels of the venous glycemia ≥ 5.6 mmol/l (100 mg/dl) or previously diagnosed type 2 DM (with values > 5.6 mmol/l or 100 mg/dl, there is recommended an oral test of tolerance to glucose, but it isn't needed for defining the MS presence).

During the last years, by carefully analyzing the elements (original or further- on - added ones) that make up the dysmetabolic syndrome, there was found out that they have a different significance. Some of them are "primary" genetic disturbances (the insulin – resistance and hyperinsulinism), others are the metabolic consequences of these disturbances and, finally, the last category includes the final complications of the syndrome, which are represented by the generalized cardiovascular disease.

Professor Ionescu – Tirgoviste, in "The Paulescu Diabetes Treatise" (2) makes the following remarks:

1) The abdominal obesity, also called "visceral" obesity, should also include the hepatic obesity (the dysmetabolic hepatopathy or the fat – loaded non – alcoholic liver) and, especially, the muscular obesity (including the one at the myocardium level). The muscular triglyceride quantity can be as high as with the normal - weight people, both in the type 2 diabetes mellitus and in other insulin – resistance states.
2) Plasmatic TG à jeun can be normal, but the post – prandial triglyceridemic curve is abnormally high and persistant.
3) Glycemia of values ≥ 110 mg/dl includes not only the "pre - diabetes" stages (IFG and IGT), but also the manifest clinical diabetes. The type II diabetes mellitus is the most illustrative clinical manifestation of the dysmetabolic syndrome (of insulin – resistance).
4) The including of the uric acid among the components of the dysmetabolic syndrome has a peculiar significance, although the increasing of the plasmatic uric acid is met with in less than 50% of the persons who present other signs of insulin – resistance. This increase expresses the alteration of the protein metabolism, which is not indicated by other available parameters; nevertheless, a normal value of the plasmatic uric acid does not exclude the existence of the insulin – resistance.
5) The presence of the hemodynamic modifications among the metabolic disturbances (as the 'dysmetabolic syndrome' name would suggest), apparently, is not a correct one. The arterial hypertension refers to the altering of the intravascular hemodynamics; yet, one could accept the idea that hypertension could be triggered by the insulin – resistance (50% of the hypertensive persons are insulin – resistant) by means of the metabolic disturbances. The hyper - tensiogenous mechanism of hyperinsulinism was connected to the increasing of the sodium and water retention at the level of the distal nephron, as a consequence of the natrium – uresis suppression induced by insulin; the phenomenon seems to be dependent the stimulation of the rennin – angiotensin – aldosterone system. These lead to the

expansion of the circulatory volume, to the increasing of the cardiac diabetes and to HTA. Another explanation of the HTA from the dysmetabolic syndrome can be connected to the presence in the hyperinsulinemic subjects of an increased sympathetic tonus, followed by vasoconstriction and the increasing of the peripheral vascular resistance. Finally, another explanation regarding the relationship between the metabolic factor and the hemodynamic one is connected to the increased endothelin production – 1 (a product that secrets the immense mass of endothelial tissue).

The initial hyperinsulinism induced by the peripheral resistance from the muscular tissue can induce a hyper expression of the endothelin – 1, of which increased production will finally lead to the accentuation of the insulin – resistance.

The NHANES III Study (National Health and Nutrition Examination Survey III, USA)(13) underlines the inconstancy of some of the syndrome components that could have an explanation. The mechanisms of controlling and adjusting a biochemical parameter (that formally belongs to a certain intermediate metabolism) can be genetically established as being vulnerable or resistant to the connected disturbances. The compensatory mechanisms can quasi completely annul or correct a biochemical abnormality.

The initial description suggested by Reaven gave the insulin resistance concept a privileged position. He supported the hypothesis that insulin resistance (and the compensatory increasing of the blood circulating insulin) is the first cause of all dis - equilibriums. Other researchers brought solid evidence that the high levels of circulating insulin (hyperinsulinism), which accompany the insulin resistance, play a part in the arterial hypertension increasing and the altering of the cholesterol and triglycerides (36).

The excess of visceral adipose or intra - abdominal tissue determines an increase of the free fat acids (FFA) in the blood circulation, a fact that leads to an increase of glycemia and, respectively, to the insulinemia (hyperinsulin-emia) increase, compensatorily, leading also to the decreasing of the receiver sensibility to insulin. The lower the insulin requirement is, owing to the low peripheral use (especially in the muscular and adipose tissue), the higher the insulin resistance. The insulin resistant fat cells (those having a volume enlarged by fat accumulation – *hypertrophic obesity*) do not remove glucose or post - prandial lipids from circulation very well, so that these remain in the blood a longer while. This lipid excess in the circulatory stream determines malfunctions in the glucose transport, leading to the insulin resistance in the liver and muscles (37).

As early as 1956, Vague mentioned the existence of the regional differences in the adipose tissue distribution. He came forward with the idea that the prevalence of diabetes, dyslipidemia and vascular complications is bigger in the obese people whose adipose mass is "centrally" disposed, especially within the abdominal area. This type of obesity was called "android" as to distinguish it from the "gynoid", peripheral one. In the abdominal obesity, the number of fat cells is normal, but their volume is high and proportional to the adiposity amount (*the hypertrophic obesity*). In the gynoid obesity, the weight excess is effected based on the number increase of the

fat cells, of which volume is, nevertheless, normal (*the hyperplasic obesity)*. The metabolic disturbances that are characteristic to the dysmetabolic syndrome are more frequently met with in the central obesity and only exceptionally in the peripheral one. The metabolism of the fat cells from the abdominal compartment differs from that of the fat cells from the gluteal – buttock one: the lipid activity (generating free fat acids) is a high one in the abdominal adipose tissue as against in the peripheral adipose one. The increased presence of free fat acids (FFA) in the portal circulation and, then, in the peripheral one has two major negative effects:

a) it induces the insulin – resistance (by the competition FFA creates against using glucose in the insulin – dependent, the decreasing of the peripheral capture of glucose with the entraining of glycemia increase that is sufficient to chronically stimulate the insulin secretion and to induce the characteristic hyper - insulinism) and

b) it increases the hepatic production of VLDL (very low density lipoproteins), particles that are rich in triglycerides, as well as the increasing of neoglucogenesis and of the glucose hepatic production, major disturbances in the dysmetabolic syndrome).

The disturbing of the plasmatic lipids within the dysmetabolic syndrome represents one of the main factors invoked for explaining the increased frequency of vascular complications recorded in these patients. The main recorded lipid disturbances are:

a) The plasmatic TG increasing (the consequence of altering the VLDL metabolism and of the B apolipoprotein increasing);
b) The HDL – cholesterol and A aplolipoprotein decreasing;
c) Free fat acids (FFA) plasmatic increasing;
d) Small and dense LDL increasing.

The mechanism by which hyperinsulinism can induce the previously mentioned lipid modifications is a complex one. It covers an increased TG hepatic production and also a decrease in their elimination from circulation, secondary to decreasing the lipoprotein lipase (LPL). The decreasing of the LPL activity in the skeletal muscle, secondary to insulin – resistance, determines the directing of the lipoprotein flow towards the fat cells (the place of depositing the fat acids). In time, in the hepatocytes, there becomes stronger the VLDL synthesis by an increased inflow of fat acids with fat cell source. The decreasing of the plasmatic levels of the HDL – cholesterol is, mainly, the consequence of the accelerated catabolism of this group of lipoproteins (consequent to the increased activity of the hepatic lipase and the transfer protein of the cholesterol esters).

During the post – prandial period, there increase both the chylomicrons (synthesized in the intestinal mucous membrane from the absorbed food lipids), and the VLDL concentration (owing to the temporary slowing of their metabolizing). To these, there is added the mecha -nism of exaggerated free fat acids (FFA) producing in the adipose tissue, as a consequence of insulin – resistance, and which will force, by substrate excess, the increased VLDL hepatic production. According to Randle's theory of glucose/fat acid competition, the cause for the glucose consumption decrease must be looked for in the more rapid intracellular

accessing by the fat acids, which will lead to the automatic decreasing (metabolically imposed) of the glucose consumption. The relationship can be, nevertheless, reversely interpreted: the primary disturbance would be the difficult accessing of glucose (at the level of conveyance or, somewhere else, during its intracellular metabolizing), a fact that would impose the covering of the energy requisites from another source (namely, from free fat acids). The decreasing of the glucose peripheral utilization as a *metabolic disturbance* will trigger the lipid and protein adjusting modifications having an impact over all tissues.

The LDL increases within the dysmetabolic syndrome have been only occasionally reported; it is only known that, with diabetes mellitus, the small and dense LDL particles are increased, which, owing to their big contact surface, are more easily subject to oxidation.

Other researchers have indicated the fact that the hormones leptine and adiponectine can play an important role in preventing MS (38). Leptine seems to he a direct muscular and hepatic effect by intensifying fat oxidizing and lipid accumulation diminishing within these tissues (muscles and liver). Researches showed that the abdominal obesity is associated with MS to a much greater extent than the hypodermic obesity, as the abdominal fat cells secret leptine deficiency and, therefore, they cannot promote a sufficient oxidation as to prevent the hepatic, muscular and pancreatic lipotoxicity (from the beta cell level) (39).

Another theory, which would explain the losing of the sensibility to insulin, is based on the inability of the body to completely oxidize fats. When the mitochondria from the muscles and liver lose its natural ability to oxidize the fat acids, the result is a fat intracellular accumulation followed by the insulin – resistance (40). Thus, one can explain why certain subjects who are not obese ones can develop MS. This theory is supported by researches that showed the fact that older, healthy, non - obese adults presented a stronger resistance to insulin (being non - diabetic ones), by comparison with the younger subjects who presented similarities in other respects (41). The researchers speculated that losing the sensibility to insulin in elderly subjects would be the result of reducing the mitochondrial functions owing to aging. Reaven showed (9) that 25% of the persons who are healthy, non - overweight or having no impaired glucose - tolerance, present a level of insulin – resistance that is similar to that of the precocious stages of type 2 diabetes mellitus.

As part of the context of numerous definitions and systematizations suggested until at present, the relationship between MS and the insulin – resistance seems not to be fully clarified (32). The insulin – resistance is one of the many pathophysiology characteristics of obesity, especially of the central obesity. It is included into the MS nosologic framework by means of obesity and it may play an important part (3). The doubts that regard the insulin– resistance situation are determined by the practical difficulties of quantifying it; also, studies didn't confirm its decisive presence in all the subjects having a dysmetabolic syndrome (31).

Other components of the dysmetabolic syndrome are represented by biochemical markers, the list of these proliferating during

the last years, in parallel with developing the pro - inflammatory theory of atherosclerosis and of endothelial dysfunction, the two of them being common both to atherosclerosis and to the diabetic macro - angiopathy.

The International Diabetes Federation brought forth a number of other parameters that seem to be connected to MS, and that should be included into the research studies in order to ascertain the predictive power of these supplementary factors for the CV diseases and/or diabetes (34). The utilization of these factors in the research activity will also allow the modifying of the definition, if adequate, and the validation of a new clinical definition:

- General obesity
- Fat cell products: high leptine levels, low adiponectine levels
- High Apolipoprotein B levels
- High LDL – cholesterol levels
- High free fat acids (FFA) levels
- Microalbuminuria
- Proinflammatory status (high PCR, high inflammatory Citokins (TNF - $\propto$, IL -6))
- Prothrombotic status (high PAI – 1, high fibrinogen)

Instead of conclusion

I dare hope that, out of the enormous mass of biochemical results, which have not been sufficiently systemized so far, there will result an "energetic" theory that should beforehand envisage the appearance of the dysmetabolic syndrome, because, in fact, the dysmetabolic syndrome is a major off - balancing of the human body in managing its own bioenergy (production + consumption).

The symptoms of the dysmetabolic syndrome are not immediate and direct ones (of the cause – effect type), but they are shifted in time and more finely interconnected, so that, although the deteriorations are obvious, it is quite hard to establish with absolute certainty how they were got to, the decisive factors having still to be properly elucidated.

MS necessitates more thorough going studies, before its definition as a "syndrome" would be fully justified and before its clinical usability would be adequately defined.

From an anthropological point of view, the metabolic syndrome can only be defined by anthropometry, as the populational/racial anthropological studies are, for the tyme being, at an incipient stage.

Paraphrasing the eminent scientist Jean Rostand, one may say that, the more various the aggressions that the human body has to endure are, the more various the measures taken for protecting it should be.

REFERENCES

1. Ionescu-Tîrgovişte C.: Diabetologia modernă. Ed. Tehnică, Bucureşti, 1997.

2. Tremblay A., Doucet E., Obesity: a disease or a biological adaptation? Obes.Rev. 1 (2000) 27-35.

3. S.Rossnen, Paper: Obesity: the disease of the twenty-first century, International Journal of Obesity (2002) 26, suppl 4, S2-S4

4. Melvin Konner – Commentary: Evolution of our environment: will we adapt? West J Med 2001; 174: 360-361.

5. Powdermaker H., *An anthropological approach to the problem of obesity*, Food and culture: A Reader. Ed. Carole Counihan and Penny van Esterik. New York: Routledge, 1997.

6. WHO, Technical report „Obesity: preventing and managing the global epidemic". Geneva, 3-5 June 2000.

7. Merck manual of medical information, *home edition, 2006*

8. AFERO, ALFEDIAM, SNDLF, Recommandations pour le diagnostic, la prevention et le traitement de l'obesite, Cah. Nutr. Diet. Suppl. 2 (1998). Diabete Metab. 24 (1998), 1-48.

9. Friedman J., Obesity in the new millennium. Nature 404 (2000) 632-634.

10. Kopelman P., Obesity as a medical problem. Nature 404 (2000) 635-643.

11. Ionescu-Tîrgovişte C., 2004. Tratat de Diabet Paulescu, Ed. Academei Române, pg701-707.

12. Arnaud Basdevan, Daniel Ricquie, *Pour une approche scientifique de l'obésité* Coll.Annales de l'Institut Pasteur, Paris 2003

13. Choo V. WHO reassesses appropriate body-mass index for Asian populations. The Lancet, Jul 2002 20; 360(9328): 235.

14. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000 May 6;320(7244):1240-3.

15. Poskitt, EM. Body mass index and child obesity: are we nearing a definition? Acta Paediatr, May 2000; 89(5): 507- 509.

16. Rosner B, Prineas R, Loggie J, Daniels SR. Percentiles for body mass index in U.S. children 5 to 17 years of age .Int J Obes Relat Metab Disord, Oct 2001;25(10):1517-24.

17. Rolland-Cachera MF, Cole TJ, Sempe M, et al. Body Mass Index variations: centiles from birth to 87 years. Eur J Clin Nutr, Jan 1991;45(1):13-21.

18. Chinn S, Rona RJ. International definitions of overweight and obesity for children: a lasting solution? Ann Hum Biol 2002 May-Jun;29(3):306-13.

19. Sorensen H., Sabroe S., Rothman K., Gillman M., Fischer P., Sorensen T. Relation between weight and length at birth and body mass index in young adulthood: cohort study. Brit Med J 1997; 315: 1137.

20. Barry Atkinson – *Obezitatea între a fi şi a nu fi*, edit. Alex-Alex 2001

21. Whitaker R., Wright J., Pepe M., Seidel K., Dietz W. Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med 1997; 337:869-873.

22. Réunions des Comités régionaux de l'OMS en 2005, Bucureşti 12 septembrie 2005. Obezitatea: o provocare pentru regiunea europeană a OMS. Update vol.III, nr.12, oct.2005, pg.104.

23. Martorell R., Khan L., Hughes M., Grummer-Strawn L., Obesity in women from developing countries, Eur.J.Clin.Nutr. 54 (2000), 247-252.

24. Obesity and Overweight: Frequently Asked Questions. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/nccdphp/dnpa/obesity/faq.htm; 2002.

25. Hickey MS, Israel RG, Gardiner SN, et al. Gender differences in serum leptin levels in humans. Biochem Mol Med. 1996; 59(1): 1-6.

26. International Journal of Obesity (2002) 26, suppl 4, S8-S10

27. Baskin M, Ard J., Franklin F., Allison D. Prevalence of obesity in the United States, Obes Rev 2005, feb.6 (1); 5-7.

28. Flegal M et al. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002; 288:1723-1727.

29. Freedman DS et al. Trends and correlates of class 3 obesity in the US from 1990 through 2000 JAMA 2002; 288:1758-1761.

30. The Merck manual of diagnosis and therapy 18th edition 2006, Merck Research Laboratories

31. Prof.Dr. Ioan Drăgan, *Cei "50 H"inamici ai sănătăţii – Obezitatea,* edit. Bogdana, Bucureşti 2001, pg.154

32. World Health Organization (2003) – Global strategy on diet, physical activity and health.

33. IOTF Childhood Obesity Report May 20.

34. Ebbeling C., Pawlack D., Ludwig D., Childhood obesity: public health crisis, common sense cure. Lancet 360 (2002) 473-482.

35. Astrup A., Toubro S., Raben A., The role of energy expenditure in the development of obesity, in: Guy-Grand B., Ailhaud G. (eds). Progress in obesity research 8, Montrouge, John Libbey, 1999, p.459-465.

36. Levin B.E., Metabolic imprinting on genetically predisposed neural circuit perpetuates obesity, Nutrition 16 (2000) 909-915.

37. Penicaud L., Cousin B., Leloup C., Lorsignol A., Casteilla L., The autonomic nervous system adipose tissue plasticity and energy balance. Nutrition 16 (2000) 903-908.

38. Van Baak M., The peripheral sympathic nervous system in human obesity, Obe.Rev. 2 (2001) 3-21.

39. L'obésité – Le Journal de CNRS nr.177, octobre 2004

40. Polonsky K., Given B., Van Cauter E. Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. *J Clin Invest 1988*; 81: 442-448.

41. Hellstrom L, Wahrenberg H, Hruska K, Reynisdottir S, Arner P. Mechanisms behind gender differences in circulating leptin levels. J Intern Med. 2000;247(4):457-462.

42. Farooqi I et all., Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med 1999; 341: 879-884.

43. Schwartz M, Woods S., Seeley R., Baskin D., Central nervous system control of food intake. Nature 404 (2000) 661-671.

44. Campfield L et al.: Mouse OB protein: Evidence for a peripheral signal linking adiposity and central neural networks. Science 269: 546, 1995.

45. Liuzzi A, Savia G, Tagliaferri M, et al. Serum leptin concentration in moderate and severe obesity: relationship with clinical, anthropometric and metabolic factors. Int J Obes Relat Metab Disord. 1999; 23(10): 1066-1073.

46. Roca P, Proenza AM, Palou A. Sex differences in the effect of obesity on human plasma tryptophan/large neutral amino acid ratio. Ann Nutr Metab. 1999; 43(3): 145-151.

47. Stephen O'Rahilly, I.Sadaf Farooqi. Genetics of obesity, Philosophical Transactions of the Royal Society B: Biological Sciences, Volume 361, Number 1471 / July 29, 2006, pg. 1095-1105.

48. Bell G, Walley A, Froguel P. The genetics of human obesity, Nat Rev Genet 2005; 6: 221-234.

49. Friedman JM, Leibel RL, Bahary N: Molecular mapping of obesity genes. Mamm. Genome, 1:130-144, 1991.

50. Rankinen T., Perusse L., Weisnagel SJ., Snyder E., Chagnon Y., Bouchard C., The human obesity gene map: the 2001 update. Obes.Res. 2002; 10: 196-243.

51. Barsh G., Farooqi I., O'Rahilly S. Genetics of body-weight regulation. *Nature 2000*; 404: 644-651.

52. Ulijaszek S. Obesity: a disorder of convenience, Obesity Reviews (2007) 8 (suppl.1), 183-187.

53. Farooqi I, O'Rahilly S. Monogenic obesity in humans, Ann Rev Med 2005; 56: 443-458.

54. Obesity Research 12:88s-101s (2004)

55. Meyre D et all. Variants of ENPP1 are associated with childhood and adult obesity and increase the risk of glucose intolerance and type2 diabetes. Nat Genet 2005; 37:863-867.

56. Levine JA, Lanningham-Foster LM, McCrady SK, Krizan AC, Olson LR, Kane PH, Jensen MD, Clark MM. *Interindividual variation in posture allocation: possible role in human obesity.* Science 2005;307:584-6. PMID 15681386.

57. Lopez R. *Urban sprawl and risk for being overweight or obese.* Am J Publ Health 2004;94:1574-9. PMID 15333317.

58. Swinburn B., Egger G., Raza F. Dissecting obesogenic environments: the development and application of a framework for identifying and prioritizing environmental interventions for obesity, Prev Med 1999; 29: 563-570.

59. Drewnowski A., Darmon N. The economics of obesity: dietary energy density and energy cost, Am J Clin Nutr 2005; 82: 265S-273S.

60. Sturm R. Childhood obesity: what we can learn from existing data on societal trends, part 2. Prev Chronic Dis 2005; 2: A20.

61. Philippe Aries, Georges Duby, *Istoria vieţii private*, vol. V, edit. Meridiane, Bucureşti 1995, pg.333-359.

62. West KM, Kalbfleish JM: Influence of nutritional factors on prevalence of diabetes. Diabetes, 20:99, 1971.

63. Rolls E, Understanding the mechanisms of food intake and obesity. Obesity Reviews (2007) 8 (suppl. 1), pg 67-72.

64. Lovejoy JC. The influence of sex hormones on obesity across the female life span. J Womens Health. 1998;7(10):1247-1256.

65. Harrison 14th edition – Principiile medicinei interne, vol. I, pg.269, Teora 2001.

66. Eric A. Finkelstein, Ian C. Fiebelkorn and Guijing Wang, State-Level Estimates of Annual Medical Expenditures Attributable to Obesity. *Obesity Research* 12:18-24 (2004).