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REFLECTION

# Once again, what's in a name? Redefining the concepts of the metabolic syndrome and obesity phenotypes. Part I

*Una vez más, ¿qué hay en un nombre? Redefiniendo los conceptos del síndrome metabólico y los fenotipos de la obesidad. Parte I*

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## INTRODUCTION

What's in a name? –inquired young Juliet, the Shakespearian universal icon of passionate love. Then she herself answered: «that which we call a rose by any other name would smell as sweet», implying that doesn't matter how we denominate things or persons, they are what they are intrinsically and not something else. While this assertion is probably true in poetry or drama, it is not equally accurate in science and medicine, which demand sharply precision of terms and proper use of them. The necessity of name things, persons or places has been an indispensable task, since the dawn of human history. In medicine (as in other fields of rational knowledge), common logic, as well as semantics and scientific language, need neat operational definitions to identify, classify, enclose, and restrict in recognizable segments, simple or complex biological and clinical concepts or phenomena. In this order of ideas, when we pronounce or write the term «diabetes mellitus type 2», everybody in every place, since a Nobel prize winner to the humblest third world physician, and from Alaska to Timbuktu, should have the same concept and the same understanding of what are we talking or writing about. There is no way to confound this disease with other one, including those whose names look alike, as diabetes insipidus. Unfortunately, in one of the most lethal, prevalent and costly human diseases, overweight and obesity (O/O), and their common companion, the so-called metabolic syndrome (MS), confusion, contradictions and ambiguity rule the scene. This article tries to put into discussion among the members of our community some conclusions of the expert group on obesity and MS of our Association (Asociación Nacional de Cardiólogos de México), aimed to the clarification of basic concepts and paradigms around the biological and clinical complexity of O/O and MS. We are aware of the difficulties involved in the modification of a term (MS), deeply inserted in contemporary medical mores and conventions, that have even take root in popular imaginary, but we think that redefinitions based on scientific concepts would help to a deeper understanding, and in consequence, to a better prophylaxis and treatment of these threatening conditions.

### From darkness to chaos: critical vision of the history of metabolic syndrome

The history of the MS is one plagued of controversies, chiaroscuros, ups and downs, and contradictions. Gerald Reaven,[1] in his now famous Banting Lecture 1988, in the midst of a dense and overloaded presentation, affirmed that… «*based on available data, it is possible to*

*suggest that there is a series of related variables –syndrome X- that tends to occur in the same individual and may be of enormous importance to the genesis of CAD [coronary artery disease]. These changes include resistance to insulin-stimulated glucose intake, hyperglycemia, hyperinsulinemia, an increased plasma concentration of VLDL triglycerides, a decreased plasma concentration of HDL-chol, and high blood pressure*»… It has to be said that in this original description there is not a single word about obesity, and although several of Reaven's epigones have stated that it was implicit in the concept, the truth is that the role of obesity in the pathophysiology of the MS was added later in other papers written by Reaven and his group.[2] To top it all, the term «syndrome X» – a fallacious and confuse locution- had been coined by Kemp, several years before, to identify patients with anginal pain and normal coronary arteries.[3] Anyhow, Reaven is considered the discoverer of the link between insulin resistance with diabetes and coronary heart disease. It is true that the connection among visceral adiposity, diabetes and heart and vascular disease had been found by several authors, decades or centuries ago. The genial anatomist and pathologist Giovanni Battista Morgagni,[4] in 1765, based in ingenious clinical-pathological correlations, come upon that visceral obesity was related to (in that time) unrecognized arterial and heart ailments, as well to stroke and urinary calculus. Curiously, exalted Italian nationalist authors of our time have exaggerated the contributions of this great pathologist, stating that he was the first to relate visceral obesity to hypertension, hyperuricemia, atherosclerosis and obstructive sleep apnea syndrome, diseases or conditions that had not been yet identified in those ancient times. Among many others who built the scaffold of our knowledge in these matters, we have to remember the Romanian physician Paulescu who stated in the remote 1920's that «obesity and fat diabetes represent two consequent phases of the same pathological process»; the Swedish author Eskil Kylin that in 1923 described a group of obese, hyperglycemic, hypertensive and hyperuricemic patients; the US physician WE Preble, who informed in 1923, based on the data from 1,000 patients, that overweight increases the risk of diabetes, as well as heart, arterial and kidney diseases; the Spaniard scholar and endocrinologist Gregorio Marañón who was one of the first to link hypertension to diabetes in 1927, and prominently, in 1947, the work of the French physician Jean Vague, who was the first to link upper body adiposity (predominantly in male subjects) with the development of diabetes and cardiovascular complications. Italians Avogaro and Crepaldi, in 1965, also described a syndrome intertwining hypertension, hyperglycemia, and obesity, and more recently, in 1980, Albrink signaled several conditions like obesity and hypertriglyceridemia, as factors that increased the risk for coronary artery disease.[5-8] The term «metabolic syndrome» was indeed coined by a German researcher, Hermann Haller, as far as in 1975.[9] He and his group stated that the combination of risk conditions (obesity, hypertension, dysglucemia, dyslipidemia, hyperuricemia, and the like) were not aggregated in some individuals by mere chance, but probably because they were the consequence of a common primary metabolic disturbance. They also pointed out that this pathological conglomeration increased cardiovascular risk and were probably the first to find the relation of these metabolic disarrays with hepatic steatosis.[10] Many of these works, in general, had been circumvented or belittled by many authors and reviewers. Certainly, this fact would not be the only example in modern medicine of how discrimination despises the valuable contributions of many non-English speaking authors and even some English-speaking researchers of lesser renown. Meisinger,[10] in a letter appeared in the journal Clinical Chemical, without accusing Reaven or anybody to look down Haller work, just described the extraordinary contributions of this German physician, including the original coining of the term. In a curiously touchy response, Reaven,[11] using also the Shakespearian quote that name this article, asserted that no matter who had been the inventor of the name, his own outstanding contribution was the concept, based in a long-range research, that insulin resistance of insulin-sensitive tissue like muscle and adipose tissue, was the common pathophysiological abnormality behind the

syndrome, and that the functional defects, insulin resistance and secondary hyperinsulinism, were the cause of its diagnostic elements and their cardiometabolic consequences, i.e. type 2 diabetes (DM2) and cardiovascular diseases (CVD). Reaven also remembered that long time before his proposal of the «syndrome X», he and his group found that patients without DM2 but with a history of myocardial infarction had fasting hyperglycemia, as well as abnormal oral glucose tolerance tests and hypertriglyceridemia. Since that time, they thought that all those disturbances leading to coronary heart disease were secondary to an unknown fundamental defect, more recently unveiled as insulin resistance. Although some reviewers awarded the coining of the term «insulin resistance» to a Viennese physician named Wilhelm Falta,[12] both the author and his presumed article seem to be somehow phantasmagorical, because nobody knows for sure anything about them. Reaven,[13] whereas recognized that British physician Harold Himsworth, in the remote years of 1936-1939, had stated that «*diabetes mellitus is a disease in which the essential lesion is a diminished ability of the tissue to utilize glucose*», questioning the accepted paradigm that DM was always characterized by an absolute defect of insulin secretion and pointing out the possibility that diabetes could be caused as well by an inefficient peripheral action of the insulin. He differentiated insulin sensitive-diabetes (due to the lack of endogenous insulin) from insensitive-diabetes (originated by decreased tissue insulin sensitivity). The introduction of radioimmunoassay techniques to measure serum insulin concentrations in the sixties of the last century,[14] allowed Nobel prize-winners Yalow and Berson to define insulin resistance as a «state in which a greater than normal amount of insulin is required to elicit a quantitatively normal response».[15,16] Then, it was recognized that many patients with DM2 had indeed higher levels of insulinemia. A decade later, the insulin receptor was characterized, as well as the nature of both insulin responsive substrates (IRS) and the transporters proteins of glucose (GLUT), along with the entire intracellular signaling cascade brought out by the interaction between insulin and its receptor, giving us a more comprehensive understanding of the considerably complex carbohydrate metabolism and insulin biological actions.[17] Later on, other rather colorful and dramatic but imprecise denominations were introduced to describe the aforementioned conglomerate: deadly quartet, X plus syndrome, visceral fat syndrome, hypertriglyceridemic waist, secret killer, plurimetabolic syndrome, cardiometabolic syndrome, Reaven syndrome, beer belly syndrome, etc.[18-24] In this context, the name of «insulin resistance syndrome» arose. Although the concept or insulin resistance/hyperinsulinism was in the medulla of Reaven[1] and Ferrannini[25] works, was Haffner who probably introduced in the first place the term «insulin resistance syndrome»,[26] which for unclear reasons did not catch on the medical imaginary. Anyhow, Reaven and Ferraninni seminal studies had laid the foundations of several physiologic and clinical paradigms: 1) Insulin resistance increases the risk of DM2. 2) Many lean patients with high blood pressure, as well as the majority of patients with DM2 are insulin resistant. 3) Secondary hyperinsulinism is the cause of the deep lipid disarrangement called lipid triad, and 4) Hyperinsulinism is a homeostatic attempt to maintain carbohydrate metabolism, preventing the development of hyperglycemia but overloading and then fatiguing insulin-producers cells, just to the point that pancreatic reserve is wasted, yielding to the burst of DM.

In 1998, the World Health Organization (WHO) provided the first working definition of MS, and a year later a modified, but still rather cumbersome and impractical version, was rendered *(Table I)*.[27]

Because these criteria were almost impossible to fulfill in real life medicine, the interest in diagnosing MS decayed. But in 2001, the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) was published, providing a simplified, clinical-oriented, and easy to carry through definition *(Table II)*.[28]

The coexistence of $\geq 3$ of these factors defines the metabolic syndrome.

In the conference convened by the National Heart, Lung, and Blood Institute and the American

**Table I. 1999 WHO diagnostic criteria of metabolic syndrome.**

| Insulin resistance (obligatory) identified by: |
|---|
| Type 2 diabetes, or impaired fasting glucose or for those with normal fasting glucose levels (< 110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions, plus two or more of the following:<br>Obesity: defined as BMI > 30 kg/m$^2$ or waist/hip ratio (WHR) > 0.9 in men and > 0.85 in women<br>Dyslipidemia: plasma triglyceride (≥ 150 mg/dL; ≥ 1.7 mmol/L) and/or low HDL-C (< 35 mg/dL, < 0.9 mmol/L in men and < 39 mg/dL, < 1 mmol/L in women)<br>High blood pressure: Blood pressure (BP) ≥ 140/90 mmHg, or antihypertensive medication<br>Microalbuminuria: as albumin excretion ≥ 20 µg/min or urine albumin/creatinine ratio (UACR) ≥ 30 mg/g (in casual sample) |

**Table II. 2001 ATP III diagnostic criteria of metabolic syndrome.**

| Risk factor | Operational defining level |
|---|---|
| Abdominal obesity (waist circumference) | |
| Men | > 102 cm |
| Women | > 88 cm |
| Triglycerides | ≥ 150 mg/dL |
| HDL-C | |
| Men | < 40 mg/dL |
| Women | < 50 mg/dL |
| Fasting glucose | ≥ 110 mg/dL |
| Blood pressure | ≥ 130/85 mmHg |

Heart Association were stand out six relevant abnormalities which explain the pathogenic power of the risk factor agglomerate: Abdominal obesity, atherogenic dyslipidemia (lipid triad), raised blood pressure or frank systemic arterial hypertension, insulin resistance, hyperinsulinism and glucose intolerance, chronic inflammatory state, and prothrombotic milieu.[29] Grundy and colleagues emphasized three potential pathophysiological causes of MS: obesity, other causes of insulin resistance and finally, an ensemble of independent molecular mechanisms mediating the clinical expression of every component of the syndrome.[29] Notwithstanding the improved vision of this approach and the clinical practicality of the new definition, and although the experts of the conference had the clearest idea about the role of obesity in the genesis of both, insulin resistance and MS, the appreciation that all five components had the same weight in the diagnostic process, introduced since the beginning certain cloud of confusion. Although it is manifest that insulin resistance can be secondary to multiple causes, it is obesity the largest producer of that metabolic disarray. In fact, in his superb defense of the MS concept,[30] Grundy himself underlined that at the end of the preceding century the role of obesity in the genesis of cardiovascular diseases was not entirely recognized or accepted by the US medical community, as it also happened in the rest of the world. Therefore, the ATP III document, without avoiding the fact of the multiple causality of insulin resistance, focused its main interest in obese patients, because obesity is by far the leading cause of the main atherogenic factors: dyslipidemia, hypertension, inflammation and thrombosis. In contrast, Reaven pointed out that only 25-35% of the variability in insulin action was related to obesity or overweight.[2] In 2005, the International Federation of Diabetes (IDF) apparently straighten up the question publishing a new worldwide definition in which central obesity assessed by waist perimeter was an obligatory diagnostic element of the MS *(Table III)*.[31] The reasons for this consideration were based in the fact that central adiposity had the stronger correlations with other components of the syndrome, and as well with the genesis of CVD. Besides, the new definition recommended that the cutoff values of abdominal circumference had to be established for every nation or ethnic group. Also, the document

**Table III. 2005 IDF diagnostic criteria of metabolic syndrome.**

| Risk factor | Definition |
|---|---|
| Central<br>Waist circumference obesity<br>*(obligatory)* | Ethnic specific |
| | Plus any two of the following |
| Hypertriglyceridemia | > 150 mg/dL |
| Hypoalphalipoproteinemia (reduced | < 40 mg/dL (men) |
| HDL-C | < 50 mg/dL (women) or specific treatment for this dyslipidemia |
| Raised blood pressure | ≥ 130 mmHg (systolic blood pressure)<br>≥ 85 mmHg (diastolic blood pressure) or specific treatment of previously diagnosed hypertension |
| Raised fasting plasma glucose | Fasting plasma glucose ≥ 100 mg/dL or previously diagnosed type 2 diabetes |

a) If fasting glycemia is ≥ 100 mg/dL, oral glucose tolerance test is strongly recommended, but is not necessary to define presence of syndrome.
b) When body-mass index is over 30 kg/m$^2$, central obesity can be assumed and waist circumference does not need to be measured.

alleged that specific treatments for dyslipidemia or high blood pressure counted as alternative indicators of those risk factors. Finally, the diagnostic level of blood sugar was lessen to 100 mg/dL according with current *American Diabetes Association* (ADA) recommendations, as already had been done before to bring up to date the ATP III criteria.

This approach seemed to settle the insufficiencies of previous attempts to define MS, and also appeared to be an elegant refinement of the landmark 2001 ATP III definition. Finally, it seemed that darkness was replaced by light. But then, all of a sudden, a chaotic turmoil came to pass, because two somehow unexpected surprising events took place. First, in 2005, Raven, the same person who years before had given life and scientific reasonableness to the concept, in an article titled «The metabolic syndrome: requiescat in pace», announced the demise of the syndrome, his own creature, and declared that it was passed away and rested in peace.[32] This death pronunciation was not the result of an emotional filicide but, instead, of a thorough rational analysis of certain facts. He remembered us that behind and bellow the ATP III diagnostic criteria was not much evidence-based clinical science derived from prospective studies, but indeed, just personal reflections and opinions of a group of experts. For that reason, the ATP III document has a lot of somehow arbitrary kind of *ukases* (self-assertive or peremptory commands) no entirely supported by evidence. Why, for example, the diagnostic criteria of MS comprise just five elements? What is the reason why hyperuricemia, inflammation and several markers of thrombogenicity were put apart, despite that are integral part of the syndrome? Which is the rationale for choose three and no more or less cardiovascular disease risk factors to diagnose the MS? Where the evidence comes from to assign the same risk power to all diagnostic elements? Where are the evidences proving that all of them had an equal physiopathological relationship with insulin resistance? It could be that, like in other diagnostic criteria systems (i.e. Jones criteria for diagnosis of rheumatic fever), exist some criteria of greater weight than others (major or minor)? Furthermore, Reaven stated that the MS concept does not bring additional help in understanding the complex physiopathology of insulin resistance. Moreover, he stated also that the concept not only lacks clinical utility

to identify subjects facing higher risk of DM2 and/or CVD better than any single component, but can let pass unnoticed patients in whom MS diagnosis was not done «administratively» (because patients did not have three or more of the aforementioned criteria) but were truly high-risk subjects (for example, hypertensive patients with hypertriglyceridemia and marginal «normal» alphalipoproteinemia). However, to be fair, Reaven transferred to the ATP III authors the entire responsibility of the gross limitations of the diagnostic criteria, when he was (with his «syndrome X») the true source and inspiration of the concept. Grundy,[30,33] the main author of the ATP III document, responded sharply, that the selected five diagnostic components were chosen because all of them were part of the standard clinical practice, and that the reason for select just three elements out of the set was that «available evidence» (not cited or provided) show that individuals with three of the traits «will have most of the other components of the metabolic syndrome». This author also emphasized the fact that the classical MS diagnostic framework is not the better tool to estimate the 10-year risk of atherosclerotic cardiovascular disease, well done by many risk scales, because does not take into account, hypercholesterolemia, gender, age and smoking, which are single powerful determinants of atherosclerosis. Instead, MS identifies better those persons with high long-term risk providing the opportunity to implement in them therapeutic lifestyle changes, as well as specific pharmacological treatments of each of the components of the syndrome. This capability is maybe the main asset of the MS concept, because it is not only an identifier instrument for long-term high-risk, but even better, helps as a simple therapeutic and prognostic guide. Besides these clarifications, Grundy[30] poured more gasoline on the bonfire, challenging the paradigm that the components of MS are in all cases the expression of insulin resistance. He noticed that several investigations pointed out that inflammation and other collateral abnormalities may play a substantial role in the genesis of the syndrome. Other of the main unanswered questions is whether the atherosclerotic risk of the MS is greater than the collective sum of its components. Grundy30 states that if several risk factors are stacked up, the resultant is not the sum of the particular risk of every component, but on the contrary, the result is multiplicative, increasing the risk geometrically and not linearly, with the addition of successive factors. Besides, Grundy underlines powerfully the role of obesity in the burst of MS, signaling that «its increasing prevalence is due largely to escalating obesity». Finally, he observed that since the beginning of the story, there was a confrontation between the cardiovascular and the endocrinology fields. In general, some endocrinologists prefer the term «insulin resistant syndrome», whereas cardiologists have endorsed the term «metabolic syndrome» (and we think that both terms are equally wrong). But regardless of this debate, despite who gets upset and who has the entire or good part of the truth, clinicians and researchers over the world have continued to use the concept and its name, rightly or wrongly.

The second shocking event occurred in 2009, when a joint conference of diverse medical societies or institutions (the International Diabetes Federation Task, IDF, the National Heart, Lung, and Blood Institute, NHLBI, the American Heart Association, AHA, the World Heart Federation, WHF, the International Atherosclerosis Society, IAS, and the International Association for the Study of Obesity, IASO) convened in an attempt to reconcile differences in the definition of the MS.[34] Astonishingly, in our judgment, the more advanced definition of the IDF was annihilated, and a very similar version of the ATP III was adopted *(Table IV)*, removing the obligatory nature to central obesity. The document just asserts that «*IDF and AHA/NHLBI representatives held discussions to attempt to solve the remaining differences between definitions of metabolic syndrome. Both sides agreed that abdominal obesity should not be a prerequisite for diagnosis*». The reasons given for such regressive change are in our view, insufficient and scarce. The authors of the document, to begin with, found «complicated» to establish abdominal obesity thresholds, and also difficulties to come upon useful predictive values of abdominal obesity for both CVD and DM2. In the same context they remark that there is not sufficient evidence (from cross-sectional and longitudinal observations) for relate CVD and DM2 with specific values of waist circumference, because there are a great deal of differences among genders, inhabitants

**Table IV. 2009 harmonized criteria for clinical diagnosis of the metabolic syndrome.**

| Measure | Categorical Cut Points |
|---|---|
| Elevated waist circumference | Specific definitions for every population or ethnic group |
| Elevated triglycerides or an alternate indicator is drug treatment for elevated triglycerides | ≥ 150 mg/dL |
| Reduced HDL-C or an alternate indicator is drug treatment for this condition | < 40 mg/dL (men)<br>< 50 mg/dL (women) |
| Elevated blood pressure or an alternate indicator is antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator) | Systolic ≥ 130 and/or diastolic ≥ 85 mmHg |
| Elevated fasting glucose or drug treatment of elevated glucose is an alternate indicator | ≥ 100 mg/dL |

The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose omega-3 fatty acids presume high triglycerides. Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

of different countries or geographical areas, and ethnic groups. They are not sure if it is justified setting-up costly national clinical programs about nutrition and exercise, from a determined cut-off value of waist circumference with all this lack of evidence. To honor fairness you cannot demand such hard evidence to one factor and, at the same time, turn a blind eye with others, like the concentration of triglycerides or marginal raise of blood pressure. We know that total mortality rates and prevalence of DM2 and CVD increase exponentially with obesity, assessed with both body mass index (BMI) or waist circumference.[35,36] But, has the same predictive value a marginal high blood pressure (≥ 130/85 but less than 140/90 mmHg)? Which is the true threshold of serum triglycerides from which CVD raises? Of course, it is impossible to set-up a universal threshold for waist circumference, given account the variability of this parameter across the world, which depends of ethnicity, heritage, nutritional status and cultural and socio-economic issues. Every country has to do its homework, implementing representing and probabilistic field studies, as Mexico did.[37]

In the second part of this article, we will do a critical examination of the term «metabolic syndrome», and will propose a new denomination based in the analysis of two great data bases of our own, composed by Mexico City inhabitants pertaining to an urban middle-class.



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