EDITORIALS

The Metabolic Syndrome: a Modern Variant of Stress-Related Disease?

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The relative control of transmissible infectious or parasitic diseases witnessed during the epidemiologic transition in the 20th century as a result of the great progress in prevention and treatment (antibiotics, antiparasitic agents) has enabled the progressive eclosion of other, nontransmissible diseases. The 4 most representative of these are cardiovascular disease, cancer, obesity, and diabetes mellitus (DM). Obesity and DM share, in part, the same genetic "soil," and their expression has been hastened by the spectacular changes in lifestyle during the second half of the 20th century, and which are still taking place. In essence, these changes concern the forsaking of healthy dietary habits (diets rich in fiber, low in saturated fats and soluble sugars, and with abundant fruit and vegetables), the cessation of regular physical exercise, and the adoption of unhealthy habits, such as smoking or excessive consumption of alcohol. Obesity and type 2 DM are now so common that they warrant the descriptive designation of "diabesity." These diseases condition or facilitate the possible accumulation in susceptible persons of other metabolic diseases (dyslipidemia, hyperuricemia) and non-metabolic disorders (high blood pressure, nonalcoholic fatty liver disease, or steatohepatitis), and even the appearance of low grade inflammatory markers (C-reactive protein, interleukin 6) or stigmas of an antifibrinolytic, prothrombotic state. This accumulation, which may or may not be sequential, of such a variety of inter-related, pathophysiological changes, often due to the common link of insulin resistance, promotes and accelerates the deve-

lopment of (macro) vascular atherogenesis (a chronic, inflammatory process with its own features), and it may provoke the clinical onset of serious consequences, including ischemic heart disease, stroke, and obliterating arteritis of peripheral vessels of the limbs, especially the legs.

Historically, the concept of the metabolic syndrome (MS) is quite recent. The syndrome was characterized in clinical practice by M. Hanefeld[1] during the 1970s as the coexistence of truncal obesity, dyslipoproteinemia, glucose intolerance or type 2 DM, hypertension, hyperuricemia, hypercoagulation and fibrinolysis defects, hyperandrogenism, fatty liver, bile stones, osteoporosis, and a high incidence of cardiovascular disease. In 1987, the association of some of these components (but not obesity!) and their link with the main pathophysiologic feature of insulin resistance was named syndrome X by Reaven.[2] This seminal study triggered basic and clinical research in the field and led to the wider and more complex concept of the MS.

According to the Task Force Consensus Report on Insulin Resistance by the Spanish Society of Diabetes,[3] "insulin resistance means the reduction in the ability of insulin to exert its biological actions in typical target tissues, such as skeletal muscle, the liver, or adipose tissue. Chronic or sustained insulin resistance is currently considered to be the common basis for numerous metabolic and nonmetabolic diseases, including type 2 DM, obesity, high blood pressure, dyslipidemias, and/or cardiovascular disease." However, insulin resistance and the MS are not synonymous. The former refers to a pathophysiologic, mechanistic disease state. The latter is a descriptive phrase that underlines a clinical and epidemiologic situation with a high risk, especially a vascular risk. Insulin resistance has its best place in the field of basic biomedical research. The concept of the MS is immediately understood by clinicians, whether they are internists, endocrinologists, or cardiologists, and it is influential in the diagnostic and therapeutic decision. It helps the clinician to estimate future "risks" (e.g., cardiovascu-

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lar). Failing to distinguish between the two concepts without doubt hinders agreement on the criteria for the definition of MS, as we highlight below.

The MS is indeed complex. It is polygenic, multifactorial in origin, and the defining criteria are far from being agreed upon internationally. The World Health Organization (WHO),[4] the EGIR group (European Group for the Study of Insulin Resistance),[5] and the North American Program for the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP-III])[6,7] have all developed different sets of criteria to define the MS. In the case of the EGIR group and the WHO, the couplet insulin resistance/hyperinsulinemia is a fundamental requirement for diagnosis. The criteria proposed in the ATP-III, however, lack this couplet. Instead, they replace it by obtaining anthropometric and laboratory data that are easily acquired in clinical practice and, therefore, accessible not only in a sophisticated hospital setting (so important!) but also in the primary health care setting. Likewise, in the ATP-III the presence of central obesity is given great importance as a criterion, yet it is not dependant on the presence of diabetic insulin resistance and/or carbohydrate intolerance, as required by the WHO or the EGIR group. Universally accepted criteria are obviously necessary, since epidemiologic studies on the MS already abound worldwide. In the United States, the NHANES III study (The Third National Health and Nutrition Examination Survey),[6] undertaken in 89 locations across the United States and in which the ATP-III criteria were first postulated, discovered an overall prevalence of the MS of 22.8% in men and 22.6% in women.

In Europe,[8] following the WHO criteria (excluding diabetics), the prevalence of the MS is 23% (ranging from 7% to 33% according to age) in men and 12% (ranging from 5% to 22% for ages 40-55 years) in women. Using the EGIR definition, the prevalence figures in European countries fall slightly to 16% in men and 9.7% in women.

In Spain, the VIVA study (Variability of Insulin with Visceral Adiposity), included in the European estimations of the EGIR,[8] detected a prevalence of 19.3% according to the WHO criteria and 15.5% according to the EGIR criteria. Studies undertaken in different regions of Spain all show a common feature, the increased prevalence of MS with age. In the Canary Islands,[9] for example, the overall prevalence was 24.4%. In the rural and urban population of Segovia it was 16.3% in women and 11.8% in men, with an overall prevalence of 14.2% (ATP-III criteria). Of note in this last study[10] was the greater prevalence of MS in women as compared with men, unlike other national and European studies.

Several different variables are involved in the development of MS, independently of race, geographical conditions, social and economic status, or education.

In general, the common teaching derived from the already numerous studies available in the scientific literature is that obesity, "specifically the visceral variant," and a lower education, social, and economic status resulting in unhealthy lifestyles are the circumstances that render populations and individuals more vulnerable. The impact of visceral, or central, obesity is a determining factor, and its clinical interpretation is as immediate as the result of measuring the waist circumference, whose measurement (with a simple tape measure) should be inexcusable in daily clinical practice. Obviously, data on height and weight are also necessary. Indeed, as recently as 14 April 2005, the International Diabetes Federation, at their International Symposium in Berlín,[11] which specifically dealt with MS, had the unanimous agreement of over 4000 experts from all over the world establish that the diagnosis of this syndrome be made with the essential finding of central obesity (>94 cm for men, 80 cm for white women, other measurements for other races), and just two of any of these other criteria: *1)* hypertriglyceridemia (>150 mg/dL) or lipid lowering therapy; *2)* reduction in the serum concentration of high density lipoprotein cholesterol (<40 mg) or treatment for it; *3)* increase in systolic (>130 mm Hg) and diastolic (>85 mm Hg) blood pressure or antihypertensive therapy; and *4)* increase in plasma glucose levels in women (>160 mg/dL) or a prior diagnosis of type 2 DM. Visceral obesity is undoubtedly at center of attention. This criterion is essential, especially in older persons, for whom all studies show that the prevalence of the MS is higher.[12]

It is convenient to note that, although all the studies carried out thus far have included the analysis of the above-mentioned variables, very few studies have considered, when examining the pathophysiological and pathogenic interpretation of the MS, the psychosocial situations surrounding daily family life—family, personal or work—as predisposing factors for the development of obesity and/or one or more of the components of this syndrome, due to their more or less sustained stress and the consequences of their prolonged alteration in endocrine regulation (hypothalamus-hypophysis-adrenal axis) of general homeostasis.[13]

At this point, it is opportune to note the importance of chronic stress, with the resulting alteration in the hypothalamus-hypophysis-adrenal axis. This is Björntorp's[14] central interpretative hypothesis of the genesis of visceral obesity and its consequences, such as insulin resistance, glucose intolerance, and high blood pressure, with the negative repercussions on cardiovascular disease. Indeed, this Swedish author, who for years has been a maximum authority in the field of clinical research on obesity, postulated more than 20 years ago that psychosocial factors (anxiety, depression, or any other chronic form of stress) were determinant factors for the onset of MS. Herein lies the undoubted

interest and novelty of the large cross-sectional study reported by Alegría et al[15] in this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA. In this study the authors approached, perhaps for the first reported time, the possible impact of work in a population of active workers (7256 workers, 82% men, mean age 45 years) with different jobs (from managers to manual workers) exposed to well-defined working conditions: automobile factory and department stores. Although the study was not designed to qualify and quantify the degree of the psychosocial impact of work or of other variables (education, economic status, lifestyle) in each category of worker, the results were eloquent in the variations in prevalence. A greater prevalence was seen in manual workers (11.8%) and a decreasing prevalence in workers with more professional and intellectual involvement (office workers, 9.3%, managers, 7.7%). This group of workers had a very low overall prevalence of MS (crude prevalence, 10.2%; adjusted for age and sex, 5.8%) as compared with that found around the world in general and Spain in particular. The basic conclusion of this study is important and severe: one in 10 active workers had MS, and it suggests, although very indirectly, the impact (together with factors associated with lifestyle) of work stress in the promotion of this complex syndrome.

Stress, a combination of cognitive and behavioral biologic reactions between an individual and the environment, is often perhaps the *primum movens* in the cascade of neuroendocrine effects that promote the development of the anomalous distribution (visceral) of the adipose tissue, and the inevitable subsequent insulin resistance and hypoinsulinemia, resulting in the accumulation of cardiovascular risk factors we call the MS. To this extent, results are beginning to be reported that clearly relate certain personal situations, such as quality of life and marital happiness (in women) with the risk—the happier the less risk–of developing MS and its consequences[16] or the similar risk in persons with bad eating habits (e.g., compulsive) induced by a different quality of chronic stress. Or, in addition, the increasing pathophysiologic similarities seen between personal stress, depression, MS, and cardiovascular risk.[17] In spite of being new, the study by Alegría et al[15] has obvious limitations in design, definition criteria for MS, and even interpretation of the results that the authors expressly recognize in their paper. Nevertheless, and despite the authors' recognition, this editorial, for the benefit of all, very respectfully but unambiguously disagrees with the authors' statement that "the use of the body mass index instead of the abdominal circumference is a widely accepted modification." As reiterated in this editorial and explicitly declared in the unanimously accepted criteria from the above-mentioned 2005 Berlin Symposium, the body mass index can be disregarded as a criterion (but not as good clinical practice), but in no way can the abdominal circumference be disregarded, since what matters as an indicator of a potential (increased) cardiovascular risk factor as much as or even more so than the total amount of fat (body mass index) is its location, in the intraabdominal compartment and/or skeletal muscle.[18] This discrepancy is based solely on very abundant and sound clinical, epidemiologic, and scientific evidence, with no other extrascientific connotation.

In conclusion, the results of the MESYAS Registry, if they are confirmed in later follow-up studies with the indispensable methodologic corrections, more or less highlight the need to return to Björntorp's initial hypothesis in which psychosocial stress, together with other genetic and environmental factors, integrate the central nucleus of the group of syndromes now known as the MS. This perspective necessitates evaluating situations of stress (especially chronic stress) in everyday life and their modality (affective, socioeconomic, work, or other) as important components of this syndrome and, very probably, with no less relevance than other conventional or "new" components, such as markers of inflammation, which are also increased in depression! This renewed focus, "old wine in new wineskins," to paraphrase Julian Huxley, requires a multidisciplinary mentality to approach this modern epidemic that involves such a potentially high degree of cardiovascular death and disease, and perhaps of other diseases as well (for example cancer), and which is the paradigm of stress-related diseases in modern civilization.

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