The metabolic syndrome entanglement: Cutting the Gordian knot

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Abstract
Questions have been raised on the clinical value of the metabolic syndrome (MS). The negative opinion regarding MS is anchored basically on a separate analysis of 4 conditions: obesity, dyslipidemia, hypertension and glucose intolerance. The common denominator of these 4 sets of arguments is that they represent an utterly simplistic view of MS as a solely predictive tool of morbidity or mortality. We believe that it is inequitable to compare it with statistically constructed predictive tools, including stronger prognostic variables even unrelated to one another from the biological point of view. Several recent large meta-analyses — one of them including nearly one million patients — systematically showed that people with MS are at increased risk of cardiovascular (CV) events. MS was associated with a 2-fold increase in CV outcomes and a 1.5-fold increase in all-cause mortality rates. A very important finding was that CV risk still remained high in patients with MS but without diabetes. The presence of MS possesses a definitely predictive value, but above all it is a widely accepted concept regarding a biological condition based on complex and interrelated pathophysiological mechanisms emanating from excess central adiposity and insulin resistance. The risk factors are multiplicative, meaning that the risk of a CV disease from risk factors rises geometrically, not linearly, as the number of risk factors increases. Therefore, currently available evidences strongly support the concept of the MS as a critical clustering of CV risk factors and diabetes, representing a true and solid evolving clinical entity. (Cardiol J 2014; 21, 1: 1–5)

Key words: cardiovascular disease, dyslipidemia, hypertension, insulin resistance, metabolic syndrome, obesity, type 2 diabetes mellitus

Introduction
During the last few years, an enormous amount of articles have been published regarding a relatively new diagnostic category: the metabolic syndrome (MS). These articles have proliferated in medical literature in the fields of internal medicine, cardiology, endocrinology, metabolism, hypertension and related disciplines. Initially, in 1988 Reaven [1] proposed a conceptual framework which linked several apparently unrelated biological events into a single pathophysiological assemble. His hypothesis argued that insulin resistance triggered a common mechanism underlying the associated abnormalities of blood pressure, high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and glucose tolerance. This concept subsequently evolved to encompass a number of multiple definitions [2] established by the World Health Organization (WHO) [3], the National
Cholesterol Education Program Adult Treatment Panel III (ATP III) [4], the European Group for the Study of Insulin Resistance [5] and the International Diabetes Federation (IDF) [6]. Central obesity has been added to the above mentioned risk factors, which were ranked in different pathogenic priorities and with dissimilar cut-off points for the individual risk factors [7]. More recently, the IDF and the modified ATP III definitions have become more concordant, with the remaining difference pertaining to waist measurement [8].

However, questions have been raised concerning the clinical value of the MS [9]. Perhaps the most direct assault on the theory has been issued in a joint report [10] from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), which questions the very existence of MS. In sharp contrast, a joint position paper from the American Heart Association and the National Heart, Lung, and Blood Institute, firmly defends the concept [11].

In the present review we deal with the pros and cons of this issue. We will firstly briefly describe the main arguments against the survival of MS as an independent clinical entity. Then, we are going to offer the current evidence to the contrary, in an attempt to cut the Gordian knot around the MS entanglement.

Cons

The negative opinion regarding the syndrome is anchored on the analysis of 4 conditions: obesity, dyslipidemia, hypertension and glucose intolerance.

First, regarding obesity it may be argued that excess adiposity is not a consequence of insulin resistance, but a change that increases the likelihood that an individual will be insulin resistant. In addition, not all obese individuals are insulin resistant [12] and, as a corollary, the risk factors for cardiovascular disease (CVD) should be confined to the subset of obese individuals who are also insulin resistant [13]. Obesity, per se, in the absence of the metabolic characteristics of insulin resistance, should not increase the incidence of either CVD or type 2 diabetes mellitus (T2DM) [14].

Second, there is a highly significant relationship between insulin resistance, compensatory hyperinsulinemia, and hypertriglyceridemia [15], which is not limited to an increase in plasma TG concentrations. Thus, although various definitions of MS have selected the combination of a high plasma TG and a low HDL-C concentration as diagnostic criteria, these changes are also associated with a decrease in low-density lipoprotein (LDL) and the postprandial accumulation of TG-rich remnant lipoproteins [16]. Both high TG and low HDL-C have been shown to increase risk of CVD [17] and may develop for reasons other than insulin resistance/hyperinsulinemia.

Third, essential hypertension is intimately linked to insulin resistance/hyperinsulinemia. Firstly, as a group, patients with essential hypertension are insulin resistant and hyperinsulinemic [18]. Secondly, normotensive first-degree relatives of patients with essential hypertension are relatively insulin resistant and hyperinsulinemic as compared to a matched control group without a family history of hypertension [19]. Thirdly, hyperinsulinemia, as a surrogate estimate of insulin resistance, has been shown in population-based studies to predict the eventual development of essential hypertension [20]. These data provide substantial support for the theory that insulin resistance/hyperinsulinemia plays a role in the pathogenesis of essential hypertension [9]. On the other hand, probably no more than 50% of patients with essential hypertension are insulin resistant [21]. However, it is only this subset of patients that display the components of the various definitions of MS that render them at greatest risk for CVD [9].

Fourth, it is well established that prevalence of some degree of abnormal glucose tolerance and/or T2DM is the abnormality most closely related to insulin resistance. More than 70 years ago Himsworth and Kerr presented evidence that "a state of diabetes might result from inefficient action of insulin as well as from a lack of insulin" [22]. Nowadays it is quite clear that resistance to insulin-mediated glucose disposal is present in great majority of individuals with T2DM [23], and that insulin resistance (or hyperinsulinemia as a surrogate estimate of insulin resistance) is a powerful and independent predictor of the development of T2DM [24].

Therefore, taking into consideration the 4 claims, the criteria for the syndrome will encompass individuals with overt disease (like CVD, T2DM, hypertension), as well as with far milder forms of the same conditions. The definition will capture a spectrum of severities, and it is highly likely that a person who satisfies the diagnostic criteria with risk factor levels just over the cut point will have a much lower CVD risk than another individual with the same combination but higher risk factor levels [10].
Pros

The common denominator of the above mentioned 4 sets of arguments is that they represent an utterly simplistic view of MS as a solely predictive tool of morbidity or mortality [25]. Of course, the presence of MS possesses a definite predictive value, but first of all it is a widely accepted concept regarding a biological condition based on the complex and interrelated pathophysiological mechanisms emanating from excess central adiposity and insulin resistance. Therefore, it is inequitable to compare it with statistically constructed predictive tools, including stronger prognostic variables even unrelated to one another from the biological point of view. For example, in the criteria for MS (in contrast to Framingham score) age and LDL cholesterol (LDL-C) levels are not included, as well as a variety of strong predictors used in other risk stratification scores: previous myocardial infarction, heart failure, smoking, family history, etc. However, MS identifies additional important residual vascular risk mainly associated with insulin resistance and atherogenic dyslipidemia (low HDL-C, high TG, small dense LDL-C). Therefore, MS could be a useful additional tool in estimation of global cardiovascular (CV) risk beyond age, gender, high LDL-C or other standard risk factors.

Additionally, one of the important questions still remaining open is its predictive value: does MS forecast CV events, diabetes onset or disease progression any better than the sum of its components? For the time being, the strongest available evidence points toward a positive answer [25]. Three consecutive large meta-analyses systematically showed that people with MS are at increased risk of CV events [26–28]. The most recent and largest of them [28] included nearly 1 million patients (total n = 951,083). There, the investigators concluded that MS is associated with a 2-fold increase in CV outcomes and a 1.5-fold increase in all-cause mortality rates. That meta-analysis showed that the point estimates for CV risk were consistently higher in women than in men. In addition, a very important finding of this study demonstrated that CV risk was still high in patients with MS but without diabetes. Moreover, it was demonstrated that the syndrome predicts CV events or diabetes independently from other conventional risk factors [29, 30]. Our group has shown that MS is a strong independent predictor of mortality and morbidity in patients with acute coronary syndrome [30]. It should be specifically pointed out that our patients with hyperglycemia and MS had higher mortality rates compared with patients with the same hyperglycemia but without MS (for example 30-day mortality rates respectively 8.3% vs. 2.5%, p < 0.05).

Analyzing the progression of carotid atherosclerosis, it should be stressed that subjects with MS have higher levels of intima-media thickness (IMT) and total plaque area at follow up than those without MS. MS predicts progression of IMT in individuals below 50 years of age, but not in older age groups, suggesting thus that MS may be involved in the initial steps of the atherosclerotic process [31].

Another argument in favor of the biological soundness of MS is based on experimental research. For instance, it should be noted that GLUT4 expression, accompanied by whole-body insulin resistance and increased plasma concentration of inflammatory biomarkers was found in an animal model of MS [32], similarly, it has been observed in humans.

Even critics of the MS concept should agree that obesity, dysglycemia, dyslipidemia and hypertension coexist more frequently than predicted by mere chance. These common chronic conditions (and components of MS) have partially overlapping mechanisms of pathogenic actions mediated through common metabolic pathways. Therefore, their total combined effect could be less than the sum of the individual effects [25].

Emerging varied areas of current MS research interests include heterogeneous topics like adiponectin and biomarkers preserving endothelial health [33, 34], angiotensinogen, resistin, and leptin secretion [33], nonalcoholic fatty liver disease and liver steatosis [35], hyperuricemia [36], genetic predisposition [37], the role of adipocytokines and neurohumoral dysregulation [38]; sleep disorders and ethnicity [39], the possible ways for treatment optimization in patients with CVD [40]. Additional related matters are currently investigated, like heart rate (HR) turbulence; it has been shown that this turbulence — a well-established predictor of cardiac autonomic dysfunction — is significantly impaired in MS patients without T2DM in adults [41]. Regarding childhood and adolescence, HR variability is disturbed in children [42], and several equations have been developed in order to early identify and adequately treat MS in young populations, taking into consideration racial, ethnic and gender differences [43]. A multimarker approach to MS could further improve CV risk stratification [44].

The concept that the MS is a consequence of obesity and insulin resistance, provides a useful “life-style changes” approach for prevention and
treatment: caloric restriction, weight-loss and increased physical activity. The next step could theoretically be pharmacological interventions such as metformin, acarbose, fibrates, weight-loss drugs (like orlistat) and perhaps glucagon-like peptide-1 agonists [45] or eventual new drugs to simultaneously treat several risk factors. A third step is represented by the surgical approach. A recent study authored by Rizzello et al. [46] and performed according to the updated guidelines for meta-analyses of non-randomized studies [47] depicts several promising surgical approaches for MS, including adjustable silicone gastric banding, Roux-en-Y gastric bypass, biliopancreatic diversion and bariatric surgery.

Conclusions

Currently available evidences strongly support the concept of MS as very far of being factitious. Quite the opposite, it is a critical clustering of CV risk factors and diabetes, representing a true and solid evolving clinical entity. These risk factors are multiplicative, meaning that the risk for CVD from risk factors rises geometrically, not linearly, as the number of risk factors increases. Therefore, the total risk that MS represents is much more than a mere summation of the isolated factors [48, 49]. MS is a multifactorial syndrome, standing firstly on 2 tightly intertwined conditions: obesity and insulin resistance; obesity causes insulin resistance, and on the other hand, insulin resistance modifies adipose tissue responses to insulin and thereby recapitulates the obese state. This situation is exacerbated by the concomitant factors [11, 48]. MS prevention, recognition, treatment, and better understanding of its underlying mechanisms should become an important approach for the reduction of CVD burden in the general population. Future problem-oriented research is needed to improve and unify its diagnostic criteria, its genetic and environmental basis and the optimal medical management.

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