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EDITORIAL COMMENT

Metabolic syndrome and cardiovascular risk

Síndrome metabólica e risco cardiovascular

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The effects of isolated and associated cardiovascular risk factors have been investigated since the mid-twentieth century, but the relationship between the elements of what is now termed the metabolic syndrome (MetS) and cardiovascular risk was paid little attention until 1988, when Reaven described the role of insulin resistance in human disease, which he called syndrome X.[1] This did not include obesity, particularly abdominal obesity, which came to be considered an important component of insulin resistance syndrome, now known as MetS, the designation preferred by the American Association of Clinical Endocrinologists.[2]

Few topics have received as much attention in the cardiovascular literature over the last decades as risk prediction. The cluster of risk factors known as MetS is a major public health challenge, due to its high prevalence in the general population and its impact on the development of cardiovascular disease (CVD) and mortality.[3] However, over the last three decades the debate about MetS has intensified, and some of its aspects are still generating a high degree of interest. The existence of different definitions of MetS hampered comparisons between studies and made it difficult to determine their value in clinical practice. Harmonization of the diagnostic criteria of MetS was not an easy process, but after a new worldwide definition was published in 2005,[4] medical societies with a particular interest in this condition reached a consensus and developed a unified definition, the Joint Interim Statement (JIS), in 2009.[5] In this, a single cutoff value for waist circumference was abolished, to be replaced by ethnicity-specific national or regional cutoffs, and a platform was established to regulate the results of the investigation. Thus, the threshold for waist circumference is still not fixed.

MetS affects about 25% of the population but its impact differs according to age and gender, which influence both its prevalence and its prognostic significance.[6] In the VALSIM study in Portugal, the prevalence of MetS (27.5% overall) increased with age in both sexes up to 80 years and was higher in women aged over 50 years.[7] The most prevalent components were increased blood pressure and abdominal obesity, as in the MORGAM Project[6] and other studies. The prevalence of MetS clearly increases with age in both genders and is higher in women. Cross-sectional studies have been crucial to determining its prevalence; without them, neither the extent of the problem nor the population attributable risk could be determined, the latter depending on the relative risk (RR) or odds ratio of this clinical entity and on its prevalence.[8]

One question under discussion in the assessment of the cardiovascular risk of MetS is whether MetS is a cardiovascular risk factor beyond its individual components. The issue is important because if it is, MetS is a specific entity that must be taken into account in order to arrive at an accurate risk assessment. If the answer is no, treating individual MetS risk factors will be sufficient. In the literature there are studies which appear to show that MetS by itself has an effect and others in which the estimated effect was close to the null hypothesis using separate adjusted multivariate models. The presence of MetS is a good predictor of coronary heart disease (CHD) and stroke, although not as good

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as the Framingham Risk Score (FRS), and of type 2 diabetes, for which it is better than the FRS.[9] In a systematic review and meta-analysis of longitudinal studies reporting associations between MetS and cardiovascular events or mortality, MetS had an RR of cardiovascular events and death of 1.78 (95% confidence interval 1.58-2.00). This association, which remained after adjustment for traditional cardiovascular risk factors, was stronger in women.[10] However, this publication prompted a letter to the Editor[11] with a different conclusion, based on an analysis of three reference studies. In the Atherosclerosis Risk In Communities (ARIC) study, McNeill et al.[12] adjusted the risk associated with MetS for its components, reporting a hazard ratio (HR) of CHD of 0.91 for men and 0.71 for women, indicating that the risk of CHD associated with the syndrome was not in excess of the level explained by the presence of its individual components. In the West of Scotland Coronary Prevention Study (WOSCOPS), Sattar et al.[13] stated that possession of MetS was not a significant predictor in the presence of the effects of its individual components when investigated in a multivariate model. Finally, Schillaci et al.[14] reported an HR of 1.73, after adjustment for blood pressure as the only component of the MetS. In their reply, Gami et al. admitted that the available data were imperfect.[11] In a study based on 36 cohorts from the MORGAM Project with a 12.2-year follow-up, the CVD risk associated with MetS was higher in women than in men. Moreover, in men, the CVD risk was higher independently of age, whereas in women total CHD risk decreased significantly and the total stroke risk tended to increase (although not significantly) with older age. In women, MetS was associated with higher RR for CHD events that decreased with age, whereas RR for stroke tended to increase.[6,15] A risk profile in which RR decreases with age while absolute risk increases means that the association between cause and possible effect is weak in older individuals. The same phenomenon is also seen with traditional risk factors, such as the relationship between smoking and CHD mortality,[16] or between hypertension and stroke.[17]

In a comparison of the prognostic impact of different MetS definitions in predicting CVD, the JIS definition identified more patients with MetS, but all definitions showed higher HRs in females than in males.[18] Using information from the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based cohort study of 6776 adults free of clinical CVD at baseline, latent class analysis showed a positive association between MetS and incident CHD events in both sexes.[19] A systematic review and meta-analysis concluded that patients with MetS, but without diabetes, were still at high cardiovascular risk, with a two-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality, and that studies were needed to investigate whether the prognostic significance of MetS exceeds the risk associated with the sum of its individual components.[3]

The link between type 2 diabetes and CVD has been recognized for many years. It is clear that individuals with diabetes have a greater likelihood of developing CVD than those without.[20] Diabetes is an independent risk factor for CVD, even stronger in women, that by itself increases risk for a wide range of vascular diseases by about two-fold on average.[21] However, the risk depends on the population and on the type of cardiovascular event (CHD, stroke or peripheral arterial disease).[21–23] Of the conditions predisposing to diabetes, MetS is one of the most prevalent. Indeed, the association between MetS and diabetes is a consequence of insulin resistance and strengthens as lifespan and exposure increase. Hypertension, dyslipidemia and abdominal obesity commonly coexist with type 2 diabetes and further aggravate the risk, which is highest in people with type 2 diabetes and features of MetS.[23,24] Furthermore, diabetes confers excess mortality risk following acute coronary syndrome despite modern therapies, highlighting the poor prognosis of coronary patients with type 2 diabetes.[25] In order to prevent the development of risk factors for MetS, lifestyle changes are recommended, especially concerning diet and exercise.[26] In the presence of MetS and diabetes, in addition to other measures that may help achieve, maintain or improve levels of risk parameters such as lipids, blood pressure and blood glucose, residual risk for CVD needs to be treated with appropriate drugs, as recommended in the guidelines. The apparent inconsistency in the association of triglycerides (TG) with CHD is not unexpected, given the complexities of TG metabolism.[27]

Knowledge of the likely prognosis helps to decide on the most useful treatment,[28] among other objectives (survival, case fatality, disease specific mortality, response, etc.). In this issue of the *Journal*, Timóteo et al.[29] monitored morbidity and mortality outcomes during follow-up in a cohort study of 300 individuals according to the presence or absence of MetS and CHD. Of note are the study's characterization of the occurrence of events under study in time using Cox regression analysis and its ability to handle censored data during a mean follow-up of 6.9 years with a low dropout rate (1.3%). Despite this, the study has some limitations, including its approach to dealing with adjusted analyses of the length of follow-up covariate and to testing potential interactions between independent variables and excluding multicollinearity. Important explanatory variables were omitted, such as major risk factors including the duration of exposure to type 2 diabetes. Type 2 diabetes and MetS are common in patients with CHD or stroke and their impact also depends on duration of exposure. Patients with diabetes and MetS are not at the same point in the course of their illness, since increased blood glucose is a late and possibly terminal manifestation of insulin resistance.[5] Another limitation is that the sample was stratified into four groups, and consequently the number of some outcomes was low, so that not all differences between the groups reached statistical significance. Moreover, the plots of survival against time are shown in steps, but these steps would be smaller, and the figure would approximate a smooth curve, if the number of patients had been higher. The data do not confirm that MetS, an entity associated with increased cardiovascular risk in people without disease, is a marker of poor outcome in sick people (those with CHD in secondary prevention), but the limitations of the approach do not make this conclusion definitive.

Given the available evidence, it is unequivocal that MetS is associated with increased cardiovascular risk and even more with type 2 diabetes, an important health challenge in Europe and worldwide. It must therefore be prevented and identified early to control its components, the risk factors identified in the guidelines. Research on the risk of MetS in the area of prognosis, with the purpose of predicting the course of CVD (such as CHD) expressed as a probability that

a particular event will occur in the future, faces methodological difficulties, and no more significant contributions to clinical practice are expected. However, with regard to the cardiovascular risk associated with dyslipidemia there is insufficient evidence, as a direct causal link between TG and CHD risk has still to be demonstrated. Hypertriglyceridemia should not be considered as a single entity but rather multiple conditions (elevated chylomicrons, an increase in the TG content of very low density lipoprotein (VLDL) particles or an increase in the total number of VLDL particles) that vary in their CHD risk, and so new research is needed to categorize phenotypes of hypertriglyceridemia.[28]

Conflicts of interest

The author has no conflicts of interest to declare.

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