



EDITORIAL COMMENT

Metabolic syndrome and coronary artery disease[☆]

Síndrome metabólica e doença coronária

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Atherosclerotic cardiovascular disease (CVD) is the leading cause of death in the western world. In recent years there have been significant reductions in associated mortality, but these gains are at risk of being reversed in the future by the increasing incidence of obesity, metabolic syndrome (MS) and diabetes.

MS is defined as a cluster of metabolic risk factors that are associated with a high risk for CVD and diabetes. Its prevalence is rising worldwide, although different epidemiological studies give widely varying estimates, which may be explained by variations between geographical areas and ethnic groups, as well as differences in the definition of MS used. Based on the NCEP-ATP III criteria, the prevalence in the USA is 23.7% and in Portugal it is 27.5%.¹

The cardiovascular risk arising from different combinations of the components of MS is not uniform; each component is an independent risk factor for CVD, and they all interact synergistically, further increasing risk. This highlights the epidemiological importance of the concept of MS, which can help identify a subgroup of individuals with increased cardiovascular risk among the overall population at low absolute risk of coronary events.

Atherosclerosis, the main predisposing factor for CVD, is a process that begins in childhood and remains silent for decades. This presents the opportunity for early detection and individualized preventive measures. Despite their importance in the etiology of atherosclerosis, there are significant limitations to the use of conventional cardiovascular risk factors for identifying asymptomatic individuals

at risk. Although the various risk scores currently in use, such as the Framingham score and the SCORE project, can identify individuals at low or high 10-year risk for coronary artery disease (CAD) or stroke, most of the population are at intermediate risk, in whom the predictive power of risk factors is manifestly low. This means that many at-risk individuals are not identified and therefore not appropriately treated, while others may be wrongly classified as high risk and receive treatments they do not need.²

In order to investigate the consequences of target organ exposure to risk factors, detection of signs of subclinical or asymptomatic atherosclerosis by non-invasive imaging methods is an alternative way to assess cardiovascular risk by visualizing the disease itself. There are various recommendations to this effect,^{3–5} including the 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults, which recommends such tests to improve the discriminatory power of cardiovascular risk scores, particularly in individuals at intermediate risk.

Non-invasive imaging modalities and parameters that can identify asymptomatic atherosclerosis in various arterial territories include coronary computed tomography with assessment of calcium score, magnetic resonance imaging (MRI), carotid intima-media thickness (CIMT) and the ankle-brachial index. The most commonly used and extensively studied are calcium score and CIMT.

Although the exact prevalence of subclinical atherosclerosis is not known, the Cardiovascular Health Study⁶ reported a prevalence of 36% in women and 38.7% in men, increasing with age, while MRI studies in the Framingham Offspring Study⁷ revealed that 38% of women and 41% of men had evidence of aortic atherosclerosis. Again, the atherosclerotic burden increased with age.

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Experience has shown that assessment of the calcium score provides independent prognostic information beyond that derived from conventional risk scores, enabling reclassification of those designated as low risk and, of particular importance, determining whether those classified as at intermediate risk are in fact low or high risk. The Framingham Heart Study⁸ showed that a calcium score of zero, while not excluding the presence of significant atherosclerotic disease, was associated with an extremely low risk for cardiovascular events (0–0.6% per year), the rate being similar for both diabetic and non-diabetic patients.

CIMT uses ultrasound to visualize the carotid arteries, the presence of subclinical atherosclerosis being assessed by intima-media thickness. Several studies, including the Multi-Ethnic Study of Atherosclerosis (MESA) in asymptomatic individuals, have shown that CIMT above the 75th percentile for age, gender and race is associated with risk for myocardial infarction, stroke and cardiovascular mortality, independently of conventional risk factors.

Two prospective studies^{10,11} compared the added prognostic value of CIMT and calcium score in asymptomatic individuals. In the study by Newman et al.,¹⁰ in individuals aged over 70, CIMT and calcium score had similar predictive value for assessing CVD and CAD risk, but CIMT was better at predicting stroke, which reflects the close relationship between stroke and the territory of the carotid arteries. On the other hand, in the MESA study calcium scores more consistently predicted cardiovascular events than CIMT, a finding supported by ROC curve analysis, in which adding the calcium score to cardiovascular risk factors significantly increased the area under the curve, while CIMT showed only a minimal increase.

The ACCF/AHA guideline recommendation (class IIa) for inclusion of calcium score and CIMT in the assessment of cardiovascular risk in asymptomatic adults is largely based on the results of the MESA study,⁹ in which of those at intermediate risk, 16% were reclassified as high risk and 39% as low risk, a 55% refinement of risk classification.

The association between MS and subclinical atherosclerosis has been the subject of several small studies using non-invasive imaging techniques.¹² Holewijn et al.¹³ studied 1517 individuals aged between 50 and 70 with MS and found a significant association between asymptomatic atherosclerosis and MS, irrespective of the definition used. The information obtained from non-invasive tests appears to reflect the damage caused by risk factors as a whole. At the same time, the more MS components were involved, the more severe the subclinical atherosclerosis, and each component had a comparable impact on risk. It thus appears to be more important to identify the different components of MS than to categorize individuals as with or without MS.

On the other hand, patients with clinically manifest CVD have a high prevalence of MS. In patients hospitalized for acute coronary syndromes (ACS), the prevalence ranged between 43% and 51%.¹⁴ Some studies^{14,15} have shown a strong association between MS and its components and severity of CAD, individuals with MS presenting higher angiographic obstruction scores. The MS components most often involved were low HDL cholesterol, elevated

triglycerides and greater waist circumference, and CAD severity increased with the number of components. Patients with MS and CAD also had a worse prognosis and more impairment of left ventricular function, cardiogenic shock and need for myocardial revascularization than those without MS.

In the Medicine, Angioplasty, or Surgery Study (MASS II),¹⁵ of patients with stable CAD followed for two years, those with MS had worse outcomes and 2.5 times higher mortality independently of age, gender, smoking, LDL cholesterol and number of vessels involved; two-year mortality was 10.6% compared to 5.2% in those without MS.

Intravascular ultrasound (IVUS) is increasingly used as a complement to coronary angiography to assess the composition of atherosclerotic plaques in order to identify those that are vulnerable.¹⁶ The evidence shows that lipid-rich vulnerable plaques have a central role in the occurrence of ACS. The culprit lesion is usually minor (<50%), but IVUS studies show that atherosclerotic plaques in patients with MS have a greater lipid volume and smaller fibrous volume, which means that these plaques are more vulnerable, leading to a higher rate of ACS. In a prospective observational study in 126 consecutive patients with stable angina and with or without MS, Amano et al.¹⁷ used IVUS to show that those with MS by the NCEP-ATP III criteria were more likely to have lipid-rich plaques than those without. The individual components of MS did not influence plaque vulnerability, but patients with more than three components had more lipid-rich plaques, which is consistent with the synergistic effects of the different MS components in atherosclerosis. These results indicate that MS is significantly associated with plaque vulnerability, and the presence of MS was an independent predictor of ACS after adjustment for confounding factors and conventional and non-metabolic risk factors.

In the study by Timóteo et al. published in this issue of the *Journal*, conventional angiography was used in a prospective study of 300 patients with suspected CAD, of whom 40.5% had MS by the AHA/NHLBI criteria but not diabetes, 23.0% were diabetic, and 36.7% had neither diagnosis. The overall prevalence of MS was 55.3%. Significant CAD was present in 51.3% of the total population, 65.2% of the diabetic group, 46.3% of the metabolic syndrome group and 48.2% of the group with neither diagnosis. Of those who underwent a functional test for ischemia before coronary angiography, 88% were positive, but significant CAD was detected in only half (49%) and of these, the same proportion (49%) had neither MS nor diabetes. The authors conclude that MS does not predict CAD, although two of its components (high blood glucose and elevated triglycerides) have predictive value; diabetes, age and male gender were the strongest predictors of CAD.

The results of the study raise several questions, as the authors themselves point out. One is the high rate of false positives on non-invasive ischemia testing, since only half of the patients had significant CAD. It is also curious that in patients with MS the prevalence of CAD was lower (46.3%) than in patients with neither MS nor diabetes (48.2%).

The study does not reveal what therapy these patients received, particularly those with significant CAD, or what the outcomes were.

As the authors point out, their study reports the experience of a single center and the results differ from those of other studies, although the latter were small and somewhat controversial, given the lack of agreement as to whether MS is a risk factor for CAD in its own right or whether it has predictive value beyond the sum of its components.¹⁸

An issue that is not discussed is the importance of identifying subclinical atherosclerotic disease as early as possible in a population with a high prevalence of MS (55.3%) before symptoms appear.

As the authors acknowledge, the study would be improved by additional information on coronary plaque morphology as provided by IVUS. Assessment of the lipid content of plaques could provide a better idea of these patients' real risk.

Finally, there is the question of the large number of symptomatic patients in this population with positive ischemia tests but angiographically normal coronary arteries (around 50%). There is disagreement concerning the underlying pathophysiological mechanisms and the implications for prognosis in such cases.

The results of recent studies¹⁹ highlight the question of failure to give due weight to signs and symptoms of ischemia in the absence of obstructive CAD. Such cases are frequently labeled as atypical angina or "false positives" on non-invasive ischemia testing. However, follow-up studies show that these patients can have increased mortality and low quality of life, as well as incurring high health care costs.²⁰ These findings mean that the pathophysiological mechanisms involved need to be investigated further in order to improve diagnosis and treatment.

There are in fact various non-atherosclerotic mechanisms that can contribute to the pathophysiology of this entity.²¹ Spontaneous thrombosis, inflammation, endothelial dysfunction, microvascular dysfunction and angiogenesis have all been shown to trigger myocardial ischemia.

Coronary vasospasm, particularly in women, is an independent predictor of ischemic disease. Women are a special population in which the concept of multifactorial disease is particularly relevant.

Several authors^{21,22} have suggested that there needs to be a paradigm shift to take into account the multifactorial nature of ischemic disease and to focus diagnostic and therapeutic strategies on myocardial ischemia and not exclusively on obstructive atherosclerotic CAD. Coronary obstruction does not always imply ischemia, and conversely, the absence of obstruction does not always mean the absence of ischemia. What is important in clinical practice is to develop ways to protect cardiomyocytes from ischemia, irrespective of the underlying mechanism.

Conflicts of interest

The author has no conflicts of interest to declare.

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