EDITORIAL

Impact of metabolic syndrome on arterial elasticity

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According to the definition in the *Diccionario de la Lengua de la Real Academia Española*, a syndrome is "a group of symptoms that characterize a disease", and a disease is "a more or less severe impairment of health". Therefore, if we stick to the rigor of definitions, what we understand by "metabolic syndrome" (MS) today does not comply accurately with that definition. The concept we have about this condition is that it is a set of physical, clinical, and laboratory signs which do not "characterize a disease", but which have the capacity to anticipate –with high predictive value– the further development of cardiometabolic complications (diabetes and atherosclerosis at different locations). That is to say that the medical jargon (as in other cases) has adapted a not very accurately semantic concept, but acceptable in daily practice. The debate about whether the MS is just a combination of unrelated phenotypes still continues.

The tendency to associate cardiovascular risk factors more often than would be expected simply by chance began to spread more than 80 years ago, when Kylin described the combination of hypertension, hyperglycemia, and hyperuricemia, and their connection with cardiovascular risk. (1) The term "metabolic syndrome" was included during the 1980s, and the whole concept was boosted after the "Banting" conference, in charge of Gerald Reaven, in 1988, which was published that year in the journal *Diabetes*. (2) This emeritus Professor of Medicine from Stanford University emphasized the importance of resistance to insulin as a common denominator of clinical and metabolical manifestations, like hyperinsulinemia, glucose intolerance, increased triglycerides, reduced HDL cholesterol, and hypertension.

This group was called "X syndrome" and suggested its great relevance as precursor of diabetes and cardiovascular disease.

Since then, there was great scientific interest from basic, clinical and epidemiological research, which advanced exponentially over time. Conclusive proof of this is that a bibliographic search of the term "metabolic syndrome" performed in PubMed in February 2010 showed 29,592 bibliographic citations, almost half of them published in the last 4 years.

In an interesting study published in the present issue of the *Revista*, Paragano et al analyze the impact MS and its components may have on the arterial wall. The selected marker of arterial stiffness was the differential pressure or pulse pressure (PP). It is known that when the arterial wall is affected by disease or ageing, it modifies its mechanical properties, and thus becomes less distensible. Therefore, it loses its capacity of adapting to volume changes caused by the phases of the cardiac cycle: pressure rises during systolic ejection, and during diastole, it falls to a greater extent than in normal conditions, and therefore, PP range is wider. The authors measured the PP in 1,155 apparently healthy individuals of both sexes, and correlated it (with the corresponding statistic adjustments) with the presence of MS, and of each component in particular. The association was present for all the variables, except for the HDL cholesterol, which showed opposite correlation. (3)

As expressed by the authors, the PP is a surrogate marker of arterial stiffness, and the use of more direct indicators –such as the pulse wave velocity (PWV) comparing carotid and femoral signals– can be more accurate, since the velocity at which the pulse wave propagates through the arterial system is a direct function of wall stiffness. (4) This technique has been widely used in clinics, and we have used it, for instance, to evaluate the endothelial function through *post-ischemic hyperflow-mediated vasodilation (5), and to analyze the effect of antihypertensive agents (angiotensin-converting enzyme inhibitors) on the arterial elasticity, in addition to its antihypertensive action.* (6) If we agree that one of the basic pathophysiologic mechanisms that underlie MS is resistance to insulin and its resulting hyperinsulinemia, it is known that the latter increases the stiffness of the vessel walls. Hansen et al –among others– found a direct and independent connection between the level of insulinemia and the PWV in a large population survey in Denmark. (7)

The most original and intriguing observation reported by Paragano et al is the paradoxical effect of HDL cholesterol on the PP (HDL $\leq 40/50 = 44 \pm 3$ *vs* HDL $> 40/50 = 47 \pm 3$; $p < 0.001$), as described in Table 3. (3) This finding shows that the rise in HDL cholesterol increases PP and contradicts other experiences, in which HDL cholesterol is neutral or beneficial for the mechanical properties of the vessel walls. (8-10) There is plenty of widely known evidence that relates the increase in HDL cholesterol with cardiovascular health: not only does it promote reverse cholesterol

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transport from the peripheral tissues to the liver but also has antioxidant, antiinflammatory, antithrombotic, and profibrinolytic properties. (11) Nissen et al demonstrated that increasing HDL cholesterol level with intravenous administration of recombinant APO A-1 Milano can cause regression of atheroma plaques evaluated with intravascular ultrasound. (12) It is reasonable to accept that normalization of structural compositon of the wall should result in an improvement of its elastic properties. These pathophysiological mechanisms have their clinical expression: The analysis of four of the major American prospective studies showed that for every 1 mg/dl rise in HDL cholesterol, there is 2-3% reduction of cardiovascular risk. (13) An analysis on 1,220 consecutive individuals who went to a cardiology clinic showed that, of the five classic components of MS, low HDL cholesterol was the one most strongly associated with a history of ischemic heart disease. (14)

In conclusion, the work of Paragano et al is an important contribution, and poses a paradox that can be attributed only to chance or to mechanisms that will be clarified in future studies.

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