Metabolic syndrome: nothing more than a constellation?

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Online publish-ahead-of-print 30 March 2007

This editorial refers to 'The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns†' by J. Wang et al., on page 857.

In these last years, the scientific community made a considerable effort to understand the biology underlying cardiovascular disease (CVD), the major cause of morbidity and mortality in the developed world. From the very beginning it became apparent that several CVD risk factors were present in the same individual, and the concept of clustering risk factors was finally labelled in the 1980s by Reaven as 'Syndrome X'. This author postulated that a set of metabolic and cardiovascular risk factors—such as hypertension, hypertriglyceridaemia, low high-density lipoprotein (HDL)-cholesterol levels, and hyperinsulinaemia—could have a common aetiology based on insulin resistance, this latter also playing a pivotal role on pathophysiology of CVD. Since then, several other features were taken into account to build the so-called 'metabolic syndrome' (MetS). The first operational definition of MetS was proposed in 1999 by the World Health Organization (WHO), with hyperglycaemia and/or insulin resistance as a central feature and other greater than or equal to two related abnormalities (hypertension, dyslipidaemia, central obesity, or microalbuminuria). In 2001, the National Cholesterol Education Program (NCEP) proposed a new definition of MetS, no longer requiring glucose impairment but rather treating glucose metabolism as of equal importance with the other components. Three over five criteria were sufficient, and no one mandatory.

Up to date, six different definitions of MetS exist as described by Wang et al. in Table 1 which this editorial refers to. All include the same core criteria of central obesity, hyperglycaemia, dyslipidaemia, and hypertension, but differ as for cut-off, mandatory requirements (central obesity or insulin resistance) and inclusion of additional factors (e.g. microalbuminuria). As a consequence of uncertain criteria, a heated debate about MetS as fact or fiction came to the limelight.

Coexistence of many definitions leads to the feeling that MetS is nothing more than a container, where different criteria are clustered time-to-time. Not only, but such definitions even proceed from the activity of panels of experts, rather than from prospective epidemiological evidence, and are therefore arbitrary. Finally, it is quite difficult to compare the data published in the overabundance of studies, where different definitions have been used and different genetic background, lifestyle, and age were considered. The paper by Wang et al.† has the merit to compare in the same non-diabetic population the prevalence of MetS coming from all the six current definitions. Their analysis demonstrates that each definition arbitrarily excludes subjects that are arbitrarily included in another one, so that the different sets of people are not congruent.

MetS has increased in arbitrariness when in 2001 the NCEP decided to leave the glucocentric view that was the cornerstone of the previous criteria. Once left out any sine qua non criterion, the natural consequence was a certain degree of relativism, with all criteria rising to the same rank. The paper by Wang et al.† simply originates from this deal.

The decision to cluster equipollent criteria into a constellation called MetS is the concrete answer of epidemiologists to the wish of predicting outcome. The rational of this clustering is that subjects with more than two criteria should show higher cardiovascular mortality/morbidity than those having only two or one criteria. Unfortunately, the Wang’s paper† demonstrates this is not the case, as the predictive power of the constellation is shown not to be higher than that of its major components. Considering MetS as a risk predictor has therefore the meaningfulness of a fiction. We must be aware that, if one single criterion has the same prognostic value than greater than or equal to three aggregated criteria, using MetS is nothing more than a diversion of resources.

Why does not the aggregation work better than single covariables? At a superficial analysis this is a little surprising. This phenomenon is probably due to the fact that, as already mentioned above, aggregation leads to restriction of the field of interest, with loss of subjects and increasing specificity to the detriment of sensitivity (excess false negatives). When we base the diagnosis on greater than or equal to three criteria and we employ this definition for calculating relative risk, we actually compare subjects at very high risk (those having MetS)
with a sub-population at low-to-intermediate-to-high risk represented by those having 0, 1, or 2 criteria considered as a whole. It is obvious that the relative risk of this subpopulation is more than one, thus reducing the power of the predictive analysis.

Wang et al. took into consideration an elderly population, so stressing that in particular cohorts some criteria probably become too inclusive, creating problems. For example, as in western society, blood pressure increases with growing old while the ‘≥130/≥85’ criterion is fixed, it is only natural to find a very high prevalence of arterial hypertension in the elderly (Figure 1). When dealing with MetS in the elderly—all about all subjects finish to be considered hypertensive—the criterion ‘arterial hypertension’ is therefore emptied of any statistical power.4

Finally, a couple of words about cut-off values and continuous variables. It has been recently pointed out that all the items considered for labelling MetS are continuous, meaning that their relative risk increases linearly without any definite cut-off.5 Falsely dichotomizing continuously distributed variables are prone to error.6 If this is accompanied by fickleness of criteria, the result is misclassification of diseased subjects as healthy and vice-versa. An example is represented by those criteria that, according to clinical guidelines, became more and more inclusive. For instance, when passing from the cut-off of hypertension ‘≥140/≥90 mmHg’ (WHO, 1998–99) to ‘≥130/≥85 mmHg’ (Updated NCEP, 2005),7 in our experience +24% subjects have hypertension, and passing from ‘≥6.1 mmol/L’ to ‘≥5.6 mmol/L’ +109% have glucose intolerance, and are therefore automatically incorporated in MetS. So, as criteria become more elastic, MetS becomes more prevalent in general population. It would be a better choice to employ variables showing curvilinear relation with cardiovascular risk, making possible the identification of clear and definite inflection points. As regards dyslipidaemia, we could suggest low-density lipoprotein (LDL) cholesterol serum levels and cardiovascular mortality among 2420 men and women from general population, showing clear cut-off values with higher risk below and above a definite plasma level.8

Conflict of interest: none declared.

References