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EDITORIAL

CVD risk assessment: do we need the metabolic syndrome or better global cardiometabolic risk calculators?

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The concept of the existence of a metabolic syndrome has received considerable attention since its introduction. However, a few years after the initial proposal of the NCEP-ATP III to use five simple criteria to diagnose the metabolic syndrome in clinical practice,[1] it became evident that there was a need to further emphasize that these criteria were not meant to define the metabolic syndrome nor to assess insulin resistance but rather that they had been proposed as screening tools to help health professionals identify, in their busy clinical practice, the most prevalent form of the metabolic syndrome: abdominally obese individuals with the atherogenic dyslipidemia of insulin resistance who are also characterized by a prothrombotic, inflammatory state. As a consequence of the presence of this constellation of metabolic abnormalities, individuals identified with the clinical criteria of the metabolic syndrome were found to be at increased risk of diabetes, hypertension and cardiovascular disease (CVD).[2–9]

As a sedentary lifestyle and consumption of an energy-dense diet are major contributing factors for the development of the metabolic syndrome among those who have the relevant susceptibility gene(s), the metabolic syndrome has been proposed a crude but useful diagnosis tool to identify patients who needed to reshape their lifestyle through more physical activity/exercise and a healthier diet. However, as many prospective studies had shown that the metabolic syndrome was associated with an increased relative risk of CVD and type 2 diabetes,[10] some health professionals began considering the metabolic syndrome as a tool to predict coronary heart disease (CHD) risk. This confusion led the ADA-EASD[11] to jointly publish a critical appraisal paper of the metabolic syndrome, which spurred further discussion and debate on the relevance of this concept in the assessment and management of CVD risk: is metabolic syndrome a clinically relevant and useful concept? Is it appropriately diagnosed in clinical practice? Does its presence modify therapeutic approaches? These questions and many others were raised in a conference of the International Chair on Cardiometabolic Risk, which was held in New York on 16 December 2006.

In the paper summarizing his lecture, David Eddy addresses the importance of assessing global CVD risk. He also uses the term cardiometabolic risk to describe such global risk. One frequent criticism addressed to the metabolic syndrome is that it is an all or none diagnosis that, therefore, does not capture information on the severity of this condition. Thus, new modeling approaches are needed with variables of the metabolic syndrome treated as continuous variables. For that purpose, Eddy reviews the Archimedes mathematical modeling approach,[12,13] which had been used to evaluate the outcome of many clinical trials. In the present exercise, to model the metabolic syndrome in relation to CHD risk, the NHANES database was used. Eddy rightfully points out that to optimally discriminate for CHD risk, whichever modeling approach developed should capture as little individuals but include those who are really at increased CVD risk. Thus, to state that 30 or 40% of Americans have the metabolic syndrome certainly does not concentrate the high-risk population and is of little diagnostic value for the prediction of CVD risk. Eddy concluded by providing evidence that although the metabolic syndrome increases relative CVD risk over 30 years, the current problem with the current diagnosis of the metabolic syndrome is that it dichotomizes variables that show a continuous relationship with risk and that we therefore urgently need a better cardiometabolic risk calculator that should of course include the important contribution of classical risk factors for CVD.

In their paper, Wilson and Meigs review the evidence from the Framingham Offspring Heart Study, which was conducted from 1991 to 1995. They clearly found that the metabolic syndrome was a stronger predictor of the risk of type 2 diabetes than that of CHD, again due to the fact that the metabolic syndrome does not include all relevant CHD risk factors. They nevertheless found that the metabolic syndrome was responsible for about one-third of CVD in men and one-sixth of CVD in women. Incidentally, the principal component analysis that had been previously performed in Framingham[14] had suggested a core component of the syndrome that included abdominal obesity, insulin resistance/hyperinsulinemia and the high-triglyceride low-HDL (high-density lipoprotein) cholesterol dyslipidemia. Other components would be related to glycemia and blood pressure.

In his review of the PROCAM prospective study, Assmann and colleagues also found that the diagnosis of the metabolic syndrome increased the relative risk of CHD with a risk ratio of 2.59. However, the CHD event rate among men with the metabolic syndrome (9.6%) was not much different from the event rate predicted by the PROCAM algorithm (10.2%). Thus, it appeared that PROCAM could largely capture the risk associated with the metabolic syndrome. However, because of a correlation of $r = 0.87$ between the body mass index (BMI) and waist circumference, Assmann and colleagues used the regression of BMI over waist to estimate waist circumference in their analyses, which could be a limitation of their approach. For instance, although we have, in the population-based Quebec Health Survey, reported almost the same correlation between waist and BMI, we found a substantial variation in waist circumference within a narrow variation in BMI units, which revealed that substantial individual variation in waist exists at any given BMI value.[15] Furthermore, an increased waist circumference might be the results of overall obesity or of an excess of subcutaneous abdominal adipose tissue, which is much less of a health hazard than excess visceral fat. To address this limitation of the waist circumference measurement, we had previously proposed to simultaneously pay attention to both waist circumference and triglyceride concentrations.[16] For instance, we found that hypertriglyceridemic waist (simultaneous elevation of waist and triglyceride levels) was the form of elevated waistline truly predictive of excess visceral adiposity and related metabolic abnormalities. Thus, as the PROCAM investigators have relied on a converted BMI to assess the contribution of abdominal obesity, they may not have been in a position to properly control for the role of visceral adiposity. Further PROCAM analyses or other prospective studies will be needed to address this question. Nevertheless, results of the analyses presented by Assmann suggest that PROCAM was better than Framingham to evaluate the CHD risk of individuals with the metabolic syndrome.

Another highly relevant and large prospective cardiovascular study is ARIC, which is reviewed herein by Christie Ballantyne and colleagues. ARIC is a large, biracial population of 15 792 middle-aged individuals in which the prevalence of the metabolic syndrome was found to reach 30% of the sample. As for most other prospective studies, a clinical diagnosis of the metabolic syndrome was found to double the prevalence of CHD, differences in prevalence rates being observed between black and white subjects. The ARIC incidence data also confirmed the risk of CVD associated with the metabolic syndrome, such risk being apparently largely explained by blood pressure and HDL cholesterol. ARIC investigators also found that the risk increased with the number of criteria of the metabolic syndrome, suggesting that we need to address the issue of the severity of the syndrome, a point not covered by current recommendations. Finally, in the ARIC study, the metabolic syndrome did not further discriminate for CHD risk beyond the Framingham risk algorithm. However, the metabolic syndrome was a much stronger predictor of diabetes than CHD, a common finding in prospective studies that have examined this question.

In her paper, Wannamethee reviews the analyses conducted in the British Regional Heart Study. She also found that the metabolic syndrome was not as good as Framingham to predict CHD. However, the metabolic syndrome was better than Framingham to predict type 2 diabetes. She also observed that the absolute risk of CVD or diabetes over 20 years of follow-up was high in the presence of 4/5 criteria of the metabolic syndrome, as incidentally it was the case for individuals in the top 2/5 of the Framingham score. Some limitations of the approach used by the investigators of the British Regional Heart Study should be mentioned: they had measured BMI rather than waist circumference and non-fasting triglyceride levels were used. Nevertheless, they ended up with a prevalence of the metabolic syndrome (26%) that was well within the range reported in other studies. No evidence for an added value of the metabolic syndrome in evaluating CHD risk could be obtained in the study.

Finally, Sattar provides in his paper a critical evaluation of the metabolic syndrome concept. Although he recognizes that the metabolic syndrome has helped educate physicians on the importance of abdominal obesity as a risk factor for type 2 diabetes and CVD while contributing to spur a closer dialogue between diabetologists and cardiologists, he points out that the metabolic syndrome as currently assessed does not substantially improve the discrimination of individuals at risk of CVD. As often raised by others, one of his most vigorous criticisms relates to the dichotomy of the diagnosis (present vs absent) of the syndrome. Sattar also mentions that rather than focusing on the metabolic syndrome, we should rather carefully examine which markers could improve our ability to discriminate for CHD risk. He highlights apolipoprotein B as one of those promising risk markers. Accordingly, markers such as fasting insulin, C-reactive protein, adiponectin, and possibly some other adipokines and cytokines should receive more attention in the future although none of them (with the possible exception of C-reactive protein) appears to be ready for prime time. Regarding the risk of diabetes, Sattar argues that the suggestion of performing an oral glucose tolerance test is unrealistic and unpractical and that an initial screening could be done with simple clinical predictors such as age, sex, family history, waist girth, and possibly some simple questions about physical activity and nutritional habits. Then, among high-risk individuals, risk of diabetes could be further fine-tuned with the use of markers such as fasting glucose and triglyceride concentrations and HbA1c levels. Thus, Sattar concludes that an all or none diagnosis of the metabolic syndrome is ineffective, suggesting that further consideration should be given to our approaches to capture the risk associated with abdominal obesity.

Nevertheless, at the end of the symposium, it was felt for a variety of reasons that the metabolic syndrome has been a useful, although imperfect, concept. For instance, the

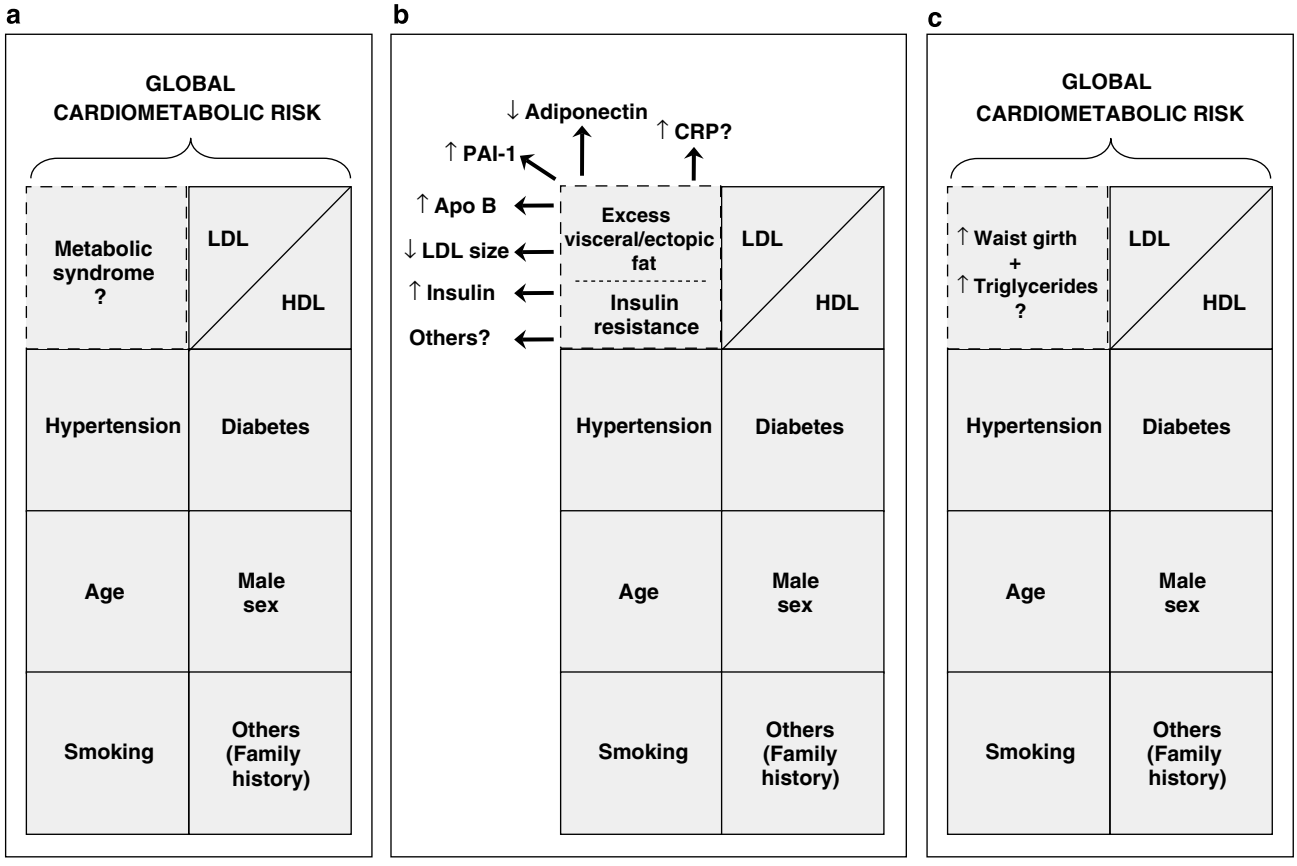

Figure 1 Although the metabolic syndrome was a milestone in our quest to better assess global cardiovascular disease (CVD) risk, the diagnosis of the metabolic syndrome cannot appropriately assess global CVD risk (global cardiometabolic risk) (**a**). Furthermore, whether its clinical diagnosis further increases CVD risk is uncertain. As the most prevalent form of metabolic syndrome is found in viscerally obese patients with excess ectopic fat and insulin resistance (**b**), another approach to global cardiometabolic risk assessment would be the development of new algorithms in which markers of visceral obesity/ectopic fat/insulin resistance found to be relevant would be included in new risk calculators that would treat risk factors/markers as continuous variables. Finally, as high-density lipoprotein (HDL) cholesterol, blood pressure and fasting glucose are NCEP-ATP III clinical criteria of the metabolic syndrome already considered in global risk assessment algorithms such as Framingham and PROCAM, it is proposed (**c**) that simple diagnosis of the most prevalent form of the metabolic syndrome could be performed in clinical practice by the presence of hypertriglyceridemic waist (↑ waist girth + ↑ triglycerides).

remarkable increase in the awareness of the medical community of the consequences of abdominal obesity and of the need to emphasize a healthier, physically active lifestyle incorporating better nutritional habits has been extremely helpful from a preventive medicine standpoint. However, for the evaluation of treatment, the current all or none metabolic syndrome assessment approach is clearly suboptimal, especially if we consider that the global absolute risk of CVD is far from being captured by the diagnosis of the metabolic syndrome, a notion that we had already emphasized in a previous review and illustrated in the Figure 1.[10]

Thus, we need to develop new models where potentially important variables will be critically analyzed as continuous variables, allowing to also assess the severity of the condition. Although the metabolic syndrome increases the relative risk of CVD, absolute risk cannot be properly assessed by the metabolic syndrome (Figure 1) and further studies will determine whether we may (or may not) need to improve our current global risk assessment algorithms.[10] Current evidence reviewed at the symposium suggested that as currently assessed, the metabolic syndrome does not add much (if at all) to global risk assessment scores obtained with Framingham or PROCAM. Physicians should measure and treat well-established risk factors and proper models should be developed with possible inclusion of relevant markers/phenotypes of visceral obesity/ectopic fat and insulin resistance (Figure 1). At the end of the day, although the metabolic syndrome was a milestone in our quest to better assess and eventually optimally manage CVD risk, it is possible that as they are, the clinical criteria of the metabolic syndrome may eventually be replaced by simple risk calculators of global cardiometabolic risk.

Conflict of interest

J-P Després has received consulting fees and/or lecture fees from Abbott Laboratories, Astra Zeneca, Fournier Pharma Inc/

Solvay Pharma, GlaxoSmithKline, Pfizer Canada Inc, Sanofi-Aventis, and Innodia. He is an advisor for MSD and Novartis, and has received research funding from GlaxoSmithKline and Sanofi-Aventis.

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