Point of View

Metabolic or Pseudometabolic Syndrome?

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Abstract

Metabolic syndrome has been proposed as a predictor of cardiovascular risk. However, such idea lacks strong scientific basis. This article reviews the evidence regarding that issue, challenging the existing paradigm of the prognostic value of metabolic syndrome.

According to Hans Christian Andersen's tale (1837), once upon a time there lived a vain Emperor who ordered from two tailors an extraordinary suit, of such unique quality that nobody had ever seen a similar one. As the tailors could not fulfill the Emperor's wish, they conceived a wonderful suit, which would be invisible to anyone who was too stupid to appreciate its quality. The Emperor himself, while trying on his new clothes, could not see them on the mirror, but pretended to see them so as not to appear stupid. Similarly, everybody could see that the Emperor was naked, but nobody admitted it, since nobody was willing to admit his own stupidity. Thus, the Emperor spent a long time naked, exposed to ridicule.

This tale explains why some medical myths last for so long, despite the lack of scientific basis. The metabolic syndrome, as an entity of great clinical value, seems to be a myth to be challenged. In reality, that entity holds a huge dissociation between its popularity and its real usefulness in medical decision making.   The metabolic syndrome can be defined as the clustering of at least three of the following five criteria: increased abdominal circumference; high triglyceride levels; low HDL-cholesterol levels; high blood pressure; and glycemia $\geq$ 100 mg/dl[1]. That concept has gained importance with the seminal study by Reaven[2], proposing a pathophysiological model in which insulin resistance/hyperinsulinemia would be the link responsible for the clustering of the cardiovascular risk factors commonly observed in clinical practice.

However, extrapolating that pathophysiological hypothesis to the creation of a concept of metabolic syndrome used to predict cardiovascular events and the development of diabetes has not been well founded, exemplifying how myths can be created. Therefore, this brief review aimed at assessing, based on scientific evidence, whether metabolic syndrome really deserves credit for that.

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A predictive model is created based on the following: (1) identification of variables associated with an outcome in cohort studies, which are submitted to (2) multivariate analysis that defines which are the independent predictors of outcome and the relative value of each one. Drawing on such data, (3) those predictors are attributed points proportionally to their force of association with the outcome, generating a risk score. That was how the classical Framingham Score was created[3].

Differently, the metabolic syndrome has not been created based on the independent association between outcome and each of those components. In a simpler strategy, experts have clustered clinical and laboratory findings based on the assumption of a single pathophysiological construct, in which insulin resistance would provide the explicative link for the different metabolic abnormalities. This has little if any relationship with risk prediction. In addition, studies have shown that the prognostic accuracy of the Framingham Score is clearly superior to that of the metabolic syndrome for predicting cardiovascular events, and that the latter does not add prognostic value to the former[3-5].

Stern et al[4] have assessed the prognostic value of those two models regarding cardiovascular events in a cohort of 1,709 non-diabetic individuals[4]. In the univariate analysis, the odds ratio of the Framingham Score was 9.7 (95% confidence interval [CI] = 6.7 – 14), clearly superior to that of the metabolic syndrome, 4.0 (95% CI = 2.8 – 5.6). Even more important, when both predictive models were tested using multivariate analysis, the Framingham Score remained with odds ratio of 9.1 (95% CI = 6.0 – 14), while the metabolic syndrome lost statistical significance (odds ratio = 1.1; 95% CI = 0.76 – 1.7). Similarly, the area under the receiver operating characteristic (ROC) curve of the Framingham Score was 0.82, as compared with 0.81 after incorporating the diagnosis of metabolic syndrome into the Framingham model. Thus, there is no incremental prognostic value in using the diagnosis of metabolic syndrome along with the Framingham Score.

Wannamethee et al[5] have reported the area under the ROC curve of the Framingham Score and the number of criteria for the metabolic syndrome in a cohort of 5,128 men of the British Regional Heart Study[5]. The Framingham Score had an area under the ROC curve of 0.73 (95% CI = 0.71 – 0.75), greater than the accuracy of the metabolic syndrome (0.63; 95% CI = 0.61 – 0.65) in predicting coronary events (p < 0.001). Likewise, in the cohort of 12,089 individuals of the Atherosclerosis Risk in Communities (ARIC) study, the area under the ROC curve of the Framingham Score was similar, with or without incorporating the definition of metabolic syndrome, in women (0.729 *vs.* 0.731) and men (0.631 *vs.* 0.634)[6].

The excessive attention given to metabolic syndrome has caused some confusion in medical reasoning. An example is the mistake of the Brazilian Guidelines on Dyslipidemia in suggesting that the presence of metabolic syndrome should reclassify patients at intermediate cardiovascular risk according to the Framingham Score to high risk[7]. In that context, it has been recommended that the presence of metabolic syndrome corrects the Framingham classification. However, it is questionable, and even surprising, that a better predictor be corrected by a worse predictor, especially when the worse predictor does not add any value to the traditional predictor[4-6].

Another argument used in favor of the metabolic syndrome is the prediction of the development of diabetes. In fact, metabolic syndrome predicts diabetes better than the Framingham Score[5]. However, when the metabolic syndrome is compared with models created to predict diabetes, the latter show better predictive capacity than metabolic syndrome[4]. Once again, that is expected, because the clustering of risk factors that define the diagnosis of metabolic syndrome is not in accordance with the scientific assumptions that have founded the creation of risk prediction models. Thus, for diabetes prediction, the most adequate are multivariate models derived from cohort studies. It is worth noting that the simple fasting glycemia is a better predictor of diabetes than the definition of metabolic syndrome. For example, in the cohort of the PROSPER study, the hazard ratio of the metabolic syndrome for predicting diabetes was 4.4 as compared with 18.4 of fasting glycemia[8].

Thus, one should question why so much emphasis on the metabolic syndrome. The excessive attention given to that syndrome originates from our culture of creating labels for diseases. Based on those labels, complementary tests, medications and complex procedures are justified. For example,

the anorexigenic drug Rimonabant (already removed from the market) had its marketing campaign based on the "cure" of metabolic syndrome. When someone is labeled as having metabolic syndrome, a procedure such as bariatric surgery might seem justifiable in someone without morbid obesity, even without the necessary scientific validation. Tests to assess myocardial ischemia might seem plausible when applied to a patient with metabolic syndrome, even when asymptomatic. And so forth. That is medicalization of society induced by labels for diseases.

Thus, returning to the tale of the Emperor's new clothes. One day, during a ceremonial parade in the streets of the village, when the Emperor passed wearing his "marvelous" clothes, one child shouted: the Emperor is naked! That child unveiled the tailors' trick, embarrassed the Emperor, and especially the people who believed in the lie or were ashamed to disagree. Some people say it was the child's innocence that allowed him/her to speak frankly. In reality, legend has it that the child was mischievous. In that case, the difference between the child and the adult was the recognition of the naked truth. Briefly, the tale of the Metabolic Syndrome teaches us that scientific knowledge is not always based on assumptions. Only questioning and scientific debate can make knowledge advance.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

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