CARDIO VASCULAR DIABETOLOGY

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# "The metabolic syndrome... is dead": These reports are an exaggeration

Alexander Tenenbaum[1,2,3*], Enrique Z Fisman[1,2]

**Abstract**

The debates continue over the validity of the metabolic syndrome concept. The continuous increment of the obesity pandemic is almost worldwide paralleled by rising rates of metabolic syndrome prevalence. Then, it seems obvious that these debates drove the need for further investigations as well as a deeper cooperation between relevant national and international organizations regarding the issue. Instead, part of the scientific community elected to totally "dismiss" the concept of the metabolic syndrome. Meanwhile, *the best available evidence* from three consecutive large meta-analyses has systematically shown that people with metabolic syndrome are at increased risk of cardiovascular events. The most recent and largest of them included near one million patients (total n = 951,083). The investigators concluded that the metabolic syndrome is associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality rates. One of the ways to hit the metabolic syndrome is an utterly simplistic view on this concept as a predictive tool only. Of course, the presence of the metabolic syndrome possesses a definite predictive value, but first of all it is a widely accepted concept regarding a biological condition based on the complex and interrelated pathophysiological mechanisms starting from excess central adiposity and insulin resistance. Therefore, it is completely unfair to compare it with statistically constructed predictive tools, including stronger prognostic variables even unrelated to each other from the biological point of view. For example, in the criteria for metabolic syndrome (in contrast to Framingham score) age and cholesterol - presumably low density lipoprotein - cholesterol (LDL-C) - levels are not included, as well as a variety of strong predictors used in other risk-stratification scores: previous myocardial infarction, heart failure, smoking, family history, etc. However, the metabolic syndrome identifies additional important residual vascular risk mainly associated with insulin resistance and atherogenic dyslipidemia (low high density lipoprotein-cholesterol (HDL-C), high triglycerides, small, dense LDL-C). Therefore, the metabolic syndrome could be a useful additional contributor in estimation of global cardiovascular risk beyond age, high LDL-C or other standard risk factors. The components of the metabolic syndrome have partially *overlapping* mechanisms of pathogenic actions mediated through common metabolic pathways. Therefore their total combined effect could be less than the summed of the individual effects. The concept that the metabolic syndrome is a consequence of obesity and insulin resistance, provides a useful "life-style changes" approach for prevention and treatment: caloric restriction, weight-loss and increased physical activity. The next step could theoretically be pharmacological interventions such as metformin, acarbose, fibrates, weight-loss drugs (currently only orlistat is practically available) and perhaps glucagon-like peptide-1 agonists. A third step should probably be kept for bariatric surgery.

The diagnostic criteria for the metabolic syndrome are not ideal. Controversy continues over the validity of its naming, as well as disagreement over its relevance as a practical clinical tool. One of the important questions which still remain open is its predictive value: does the metabolic syndrome forecast cardiovascular events, diabetes or disease progression any better than the sum of its components?

The continuous increment of the obesity pandemic is almost worldwide paralleled by rising rates of metabolic syndrome prevalence. Then, it seems obvious that these debates drove the need for further investigations as well as a deeper cooperation between relevant national and international organizations aiming to improve and unify the terms [1,2]. Surprisingly, part of the scientific community

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elected to totally "dismiss" the concept of the metabolic syndrome instead [3-5].

Meanwhile, *the best available evidence* from three consecutive large meta-analyses systematically had shown that people with metabolic syndrome are at increased risk of cardiovascular events [6-8]. The most recent and largest of them [8] included near one million patients (total n = 951,083). The investigators concluded that the metabolic syndrome is associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality rates. The meta-analysis showed that the point estimates for cardiovascular risk were consistently higher in women vs. men. A very important finding of this study demonstrated that cardiovascular risk was still high in patients with the metabolic syndrome but without diabetes.

The prognostic importance of the metabolic syndrome, compared with that of the sum of its individual components has repeatedly been challenged [5,9,10]. For example, in a cohort study of 2,815 patients [9], the risk of cardiovascular disease (CVD) mortality associated with the metabolic syndrome (HR: 2.53; 95% CI: 1.74 to 3.67) was similar to the risk associated with impaired fasting glucose (HR: 2.87; 95% CI: 1.96 to 4.20). However, it seems that most of the published reports indicate that the syndrome predicts cardiovascular events or/and diabetes independently from other conventional risk factors [11-16]. Our group has shown that metabolic syndrome is a strong independent predictor of mortality and morbidity in patients with acute coronary syndrome [16]. It should be specifically pointed out that patients with hyperglycemia and metabolic syndrome had higher mortality rates compared with patients with the same hyperglycemia but without metabolic syndrome (for example 30-day mortality rates respectively 8.3% vs. 2.5%, $p < 0.05$)!

This situation resembled the old and long- lasting discussion regarding clinical significance of insulin resistance: over the past years it has been recognized that insulin resistance is an independent risk factor for the development of type 2 diabetes mellitus, whereas its association with major cardiovascular events remained controversial. We have previously demonstrated the independent association of insulin resistance with major cardiovascular events and mortality [17]. After multivariable adjustments, measurable effect of insulin resistance was somewhat attenuated but remained significant. Similarly, insulin resistance was associated with >2-fold increased age-adjusted risk for the development of diabetes in nondiabetic subjects. After adjustment for multiple potential confounders, the prediction conferred by the insulin resistance for new diabetes was substantially attenuated, mainly after inclusion of body mass index in the model, remaining yet strongly significant. Consequently, insulin resistance and body mass index are most likely associated with diabetes development by partially (but not completely) reciprocated mechanisms.

One of the ways to hit the metabolic syndrome is an utterly simplistic view on this concept as a predictive tool only. Of course, the presence of the metabolic syndrome possesses a definite predictive value, but first of all it is a widely accepted concept regarding a biological condition based on the complex and interrelated pathophysiological mechanisms starting from excess central adiposity and insulin resistance. Therefore, it is completely unfair to compare it with statistically constructed predictive tools, including stronger prognostic variables even unrelated to each other from the biological point of view. For example, in the criteria for metabolic syndrome (in contrast to Framingham score) age and cholesterol (presumably LDL-C) levels are not included, as well as a variety of strong predictors used in other risk-stratification scores: previous myocardial infarction, heart failure, smoking, family history, etc. However, the metabolic syndrome identifies additional important residual vascular risk mainly associated with insulin resistance and atherogenic dyslipidemia (low HDL-C, high triglycerides, small dense LDL-C). Therefore, the metabolic syndrome could be a useful additional contributor in estimation of global cardiovascular risk beyond age, high LDL-C or other standard risk factors.

Moreover, even critics of the metabolic syndrome concept should agree that obesity, dysglycemia, dyslipidemia and hypertension coexist more frequently than predicted by chance. These common chronic conditions (and components of the metabolic syndrome) have partially *overlapping* mechanisms of pathogenic actions mediated through common metabolic pathways. Therefore their total combined effect could be less than the summed of the individual effects.

People with the metabolic syndrome usually pass through the phases of excessive adipogenesis (obesity), nuclear peroxisome proliferator-activated (PPAR) receptors modulation, insulin resistance, hyperinsulinemia, impaired glucose postprandial and fasting levels [2,18-22]. Fasting glucose is presumed to remain normal or borderline as long as insulin hypersecretion can compensate for insulin resistance. The fall in insulin secretion (due to pancreatic beta cells stress and damage) leading to hyperglycemia occurs as a late phenomenon and, in fact, separates the patients with metabolic syndrome from those with or without overt diabetes.

Development of insulin resistance in consequence of excess central adiposity has been considered to be key event in the origin and progression of the metabolic syndrome. It represents a complex interaction of maladaptive characteristics related to impaired insulin action at target organs and external factors such as genetics

and environment. It is likely that the molecular factors that underlie insulin resistance (mediated in part via nuclear PPAR) contribute for many of the clinical components of the metabolic syndrome, although the precise associations remain still weakly understood [2,21,23-26].

Emerging multiple areas of metabolic syndrome research interests include nowadays heterogeneous topics like as adiponectin, angiotensinogen, resistin, and leptin secretion [27-29], nonalcoholic fatty liver disease and liver steatosis [30-32], hyperuricemia [33], genetic predisposition [34,35]; the role of inflammation, interleukins and high-sensitivity C-reactive protein [36-39]; age and gender specific profiles [40,41], the possible ways for treatment optimization [42-47] and several additional matters.

The concept that the metabolic syndrome is a consequence of obesity and insulin resistance, provides a useful "life-style changes" approach for prevention and treatment: caloric restriction, weight-loss and increased physical activity. The next step could theoretically be pharmacological interventions such as metformin, acarbose, fibrates, weight-loss drugs (currently only orlistat is practically available) and perhaps glucagon-like peptide-1 agonists [48-52]. A third step should probably be kept for bariatric surgery [53,54].

In conclusion, currently available evidences strongly support the evolving concept of the metabolic syndrome as an important clustering of the cardiovascular risk factors and diabetes. Resembling Mark Twain's renowned saying [55], the reports of its death are an exaggeration. The recognition, prevention, and treatment of the metabolic syndrome and its underlying risk factors should become an important approach for the reduction of cardiovascular disease burden in the general population. However, future problem-oriented research is needed to improve and unify the diagnostic criteria for the syndrome, its genetic and environmental basis and the optimal medical management.

#### Abbreviations

CVD: cardiovascular disease; LDL-C: low density lipoprotein - cholesterol, HDL-C:high density lipoprotein-cholesterol; PPAR: peroxisome proliferator-activated receptor.

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#### Authors' contributions

Both authors have equally contributed in the conception and drafting of the manuscript and read and approved its final version.

#### Competing interests

The authors declare that they have no competing interests.

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