Metabolic Syndrome: Myth Of Reality

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EVOLUTION OF METABOLIC SYNDROME

After being given a series of names throughout the path of its evolution since 1922, when a Swedish physician named Kylin described a clustering of hypertension, hyperglycemia and gout, it is now almost universally known as “metabolic syndrome”. Other names used are Syndrome X, Cardiometabolic syndrome, Insulin resistance syndrome, Beer Belly syndrome, Reaven’s syndrome etc.

In the year of 1960 Yalow and Berson establish the concept of insulin resistance associated with obesity.

In 1967, Avogaro and Crepaldi, two Italian researcher first describes a clustering of cardiovascular risk factors (hypertension, diabetes, dyslipidemia, and obesity) all of which improve when these pts were put on hypo caloric and low-carbohydrate diet.

In 1977, Haller originally used the term metabolic syndrome for associations of obesity, DM, hyperlipoproteinemia, hyperuricemia and hepatic steatosis.

In 1988 in his Banting lecture at annual meeting of American Diabetes Association, Gerald M. Reaven proposed insulin resistance as the key mechanism and named this constellation of abnormalities as Syndrome X.

In the year 2001 NCEP-ATP III proposes diagnostic criteria for metabolic syndrome that establish cut off points for five risk factors: abdominal girth, high blood pressure, high serum cholesterol, triglycerides, and fasting glucose. Results showing 3 or more risk factors are considered to have metabolic syndrome. In 2005 International Diabetes Federation (IDF) recognizes the central obesity as important and essential component of the syndrome.

PATHOPHYSIOLOGY OF THE METABOLIC SYNDROME

Proposed pathophysiology of metabolic syndrome, if it is present at all, described in short here.

The metabolic syndrome (MS) is characterized by the variable coexistence of hyperinsulinemia, obesity, dyslipidemia, hyperglycemia, and hypertension. Other conditions associated with the syndrome include microalbuminuria, inflammation, a prothrombotic state, and fatty liver, PCOD, endothelial dysfunction.

These environmental factors probably interact with predisposing genetic backgrounds [fig.5] which are believed to be associated with 1) insulin resistance, 2) obesity, and 3) chronic low grade inflammation. Though anyone of the three can be postulated as the starting point, they are so entangled as to make sure a distinction very difficult if not impossible.

INSULIN RESISTANCE

Insulin resistance was initially proposed by Reaven as the common pathogenetic factor favoring the development of impaired glucose tolerance/type 2 diabetes, low-HDL cholesterol, increased triglycerides, and hypertension.

As adipose, muscle, and hepatic tissues become progressively more insulin-resistant, circulating FFA levels increase,
Fig. 1: Metabolic risk factors and their progression to diabetes and cardiovascular disease

Peripheral glucose disposal declines, and hepatic glucose and lipoprotein production raise. Impaired insulin action is mainly the results of impairments in the IRS-1/phosphoinositol-3 kinase pathway as depicted in fig. 2.

The cardiovascular risk associated with insulin resistance is, at least in part, mediated through the concomitant atherogenic lipid profile as described in fig. 3.

Almost 50% of hypertensive patients are insulin resistant. Ferrannini et al. (5) have analyzed the relationship between insulin sensitivity and blood pressure. Possible mechanisms by which insulin resistance and hyperinsulinemia contribute to the pathogenesis of hypertension include activation of the sympathetic nervous system and atherogenesis.

OBESITY AND CHRONIC LOW-GRADE INFLAMMATION
Abdominal obesity is certainly the most prevalent among trait of MS. Approximately 60% of people with MS have obesity as a contributing factor. Nonetheless, MS can occur in people who are not overweight. Finally, FFA can exert a toxic effect on the beta-cell, causing impaired insulin secretion and reduced beta-cell mass. The probable mechanism described in fig. 4.

REALITY OR MYTH
In the year 2005, the ongoing campaign on metabolic syndrome took a major setback when Kahn and colleagues, on behalf of ADA and EASD organizations, have suggested that the time has come for a critical appraisal of the metabolic syndrome. They claim that there is confusion about the syndrome.

ADA/EASD point out that the risks of metabolic syndrome are real, even if the terminology is questionable. They suggest using “metabolic risk” or “cardio metabolic risk” to describe the “unexpected clustering of cardiovascular risk factors related to altered metabolism.

“It’s useful as a concept, but not using the word
Fig. 2: Insulin signal transduction in vascular endothelium. Akt/PKB, Akt kinase/protein kinase B; ECM, extracellular matrix; I.R., insulin resistance; IRS, insulin receptor substrate; MAPK, Mitogen-activated protein kinase; P13-K, Phosphatidylinositol 3-kinase; SMC, smooth muscle cells.

FFA release into circulation.

**FFA are involved in insulin sensitivity and glucose metabolism.**

**TNF-α increases PAI-1 and decreases adiponectin**

**Genetics of the Metabolic Syndrome**

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**Fig. 4**

**TNF-α**

Produced by adipocytes

Acts only locally

- Circulating resistin: Unknown function. Unlikely involved in insulin resistance.
- Resistant produced by stromal cells. Released into the circulation?
- IL-6 produced by adipocytes. Released into the circulation.
- Circulating IL-6: Direct role in insulin resistance by altering insulin signaling in hepatocytes. Decreases adiponectin.

- Leptin produced by adipocytes. Released into the circulation.
- Adiponectin produced by adipocytes. Released into the circulation.

**Genetics of the Metabolic Syndrome**

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**Fig. 5:** Candidate genes for the metabolic syndrome. PPAR-γ, peroxisome proliferator-activator receptor γ; NOS3, endothelial nitric oxide synthase; ADR 3-adrenergic receptor; ACE, angiotensin converting enzyme; LMNA; lamin A/C; IL-6, interleukin-6; PTPN1, protein tyrosine phosphatase 1B. The cromosomal location is reported in paraenthesi.
The ADA/EASD paper points out specific areas of concern about how the diagnosis of metabolic syndrome is currently used. Criteria are ambiguous or incomplete, and the rationale for thresholds is ill-defined.

Ultimately, the CVD risk associated with metabolic syndrome appears to be no greater than the sum of its parts, ADA and EASD conclude. Treatment of the syndrome is no different than the treatment for each of its components. The medical value of diagnosing the syndrome is unclear, the authors say.

The authors of the ADA/EASD statement have raised a number of specific questions:

1) The clarity of the existing definition and whether it is justifiable to employ the term “syndrome” to the clustering of metabolic risk factors;
2) Whether the metabolic syndrome is a valid indicator of cardiovascular risk;
3) Whether there is enough known about the pathogenesis of the syndrome to justify including it in clinical practice;
4) Ambiguous criteria given by ATP III and IDF for clinical use, and

Now if we can find appropriate answers of these questions then perhaps we can solve the problem of “reality or myth”.

1. The Clarity of the Existing Definition and Whether It Is Justifiable to Employ the Term Syndrome to the Clustering of Metabolic Risk Factors:

A well-accepted and medical dictionary given definition of Syndrome is: “The group or recognizable pattern of symptoms or abnormalities that indicate a particular trait or disease”. Clustering of metabolic abnormalities that have provoked this debate appear to be fundamentally related to obesity and insulin resistance fits the accepted definition of a syndrome and not a disease state. ADA and EASD states that diagnostic criteria are not adequately defined to apply them into clinical practice. For this reason, ATP III took 2 steps in its effort to achieve clinical utility. First, it restricted the clinical diagnosis to simple clinical measures: waist circumference, fasting triglycerides, HDL cholesterol, blood pressure and fasting glucose. This ensured that clinicians almost anywhere in the world can readily identify an individuals. In addition, it used threshold for each of these measures that had already been defined by expert panels.

The IDF employed the same approach by maintaining ATP III thresholds for all measures except waist circumference. For this parameter, thresholds were modified according to ethnic population, which similarly had been established for these populations by expert panels based on published data.

2. Is There Enough Known About Pathogenesis of the Syndrome to Justify Including It in Clinical Practice?

Now a days much have been learned about pathophysiology of the syndrome and they are discussed in the next chapter.

3. Is the Metabolic Syndrome a Valid Indicator of Cardiovascular Risk?

Predicting Risk for Cardiovascular Disease. The 2 major clinical outcomes of the metabolic syndrome are CVD and type 2 diabetes. The relative risk for CVD varies somewhat among different reports. However, as a general rule, the risk from the metabolic syndrome for major CVD events is approximately twice as high as for those without the syndrome. For type 2 diabetes, the metabolic syndrome confers an approximate 5-fold greater risk. Finally, type 2 diabetes itself is accompanied by increased risk for CVD, and most of this increased risk is conferred by the concomitant risk factors of the metabolic syndrome. In other words, type 2 diabetes alone, independent of the metabolic syndrome, carries much less risk for CVD than when the metabolic syndrome is concomitantly present. It cannot be overemphasized that the metabolic syndrome is not an absolute risk predictor. To predict absolute risk for individuals, sometimes called global risk, it is necessary to include all of the risk factors related to the outcome. For CVD, these include age, sex, total cholesterol, HDL cholesterol, triglyceride, blood pressure, body mass index, glucose status, tobacco usage, and family history, depending on the risk-assessment algorithm employed. The metabolic syndrome is an incomplete predictor of absolute risk, and to question it for this reason represents a significant misunderstanding of its use in clinical practice.

The metabolic syndrome does not serve as a tool to define absolute risk for decisions about preventive drug therapy. The clinical utility of the syndrome for risk assessment lies in its ability to readily identify individuals who are at a relatively high, long-term risk for both CVD and diabetes and they should undergo absolute risk assessment. But once found to have the metabolic syndrome, they deserve more intensive intervention with lifestyle approaches.

4. Is the Risk the Sum of the Parts?

Whether the risk accompanying the metabolic syndrome is
greater than the sum of its parts.” There are 3 answers to this question. First, statistical epidemiologists differ as to whether multiple risk-factor conditions best fit an additive model or a multiplicative (synergistic) model. If the latter holds true, then the risk that is associated with multiple risk factors is greater than the sum of the individual risk factors. If the former is true, the risk equates to the sum of that conveyed by the individual risk factors. A sizable body of experts favors the multiplicative model. Included among these are the Framingham Heart Study investigators. If this model holds, then the risk accompanying the metabolic syndrome is indeed greater than the sum of its parts.

Second, the metabolic syndrome contains risk factors that are not commonly identified in clinical practice, e.g., prothrombotic state and proinflammatory states. Even if the appropriate model is an additive one, the risk is greater than its readily identifiable parts.

Finally, some of the so-called “independent” risk factors, e.g., blood pressure and HDL cholesterol, subsume some of the risk contained in the “hidden” risk factors of the metabolic syndrome. Thus, it cannot be assumed that all of the risk accompanying the metabolic syndrome can be reversed by lowering blood pressure and raising HDL levels, the so called independent risk factors associated with the syndrome.

5. Does Cardiovascular Prevention Require Anything More than Treatment of the Individual Risk Factors?
Clinical trials reveal that blood pressure-lowering drugs or HDL-raising therapy reduce risk less than predicted from epidemiologic studies. Thus, the prescription to just treat the independent risk factors of the metabolic syndrome does not ensure the degree of risk reduction that is implied. In addition, arguments neglect the fact that the summation of the individual CVD risk factors account for a part of cardiovascular risk, and current therapies reduce risk by only part.

This means that there is a “residual risk” that cannot be explained by the risk factors. If we are to cut into the additional CVD risk, we need to affect other factors. The metabolic syndrome is one of the components of residual risk, and is the best additional target to the standard risk factors.

The big question for the future is whether pharmacologic therapy will be found to target the metabolic syndrome specifically. In the meantime, however, we know that lifestyle modification will improve the many components of the syndrome.

REFERENCES