Clinical Use of the Metabolic Syndrome: Why the Confusion?

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Stated generally, the metabolic syndrome is a multiplex risk factor for cardiovascular disease (CVD) and type 2 diabetes that reflects the clustering of individual risk factors resulting from obesity and insulin resistance. Currently, this multiplex is thought to be composed of the following broadly stated metabolic risk conditions: atherogenic dyslipidemia, hypertension, glucose intolerance, proinflammatory state, and a prothrombotic state. Atherogenic dyslipidemia is itself an aggregate term encompassing elevated triglycerides and apolipoprotein B, increased small LDL particles, and reduced HDL.

Although the metabolic syndrome is a relatively new concept, research into the clustering of individual cardiovascular risk factors is an old enterprise. In the 1920s, investigators were reporting the occurrence of hyperglycemia, hypertension, and hyperuricema in certain groups of individuals.[1] In the 1960s, obesity and hyperlipidemia were added to this cluster.[2] Then in 1988, Gerald Reaven systematized the concept of a risk factor syndrome and suggested that insulin resistance and resultant compensatory hyperinsulinemia could mechanistically explain most of this clustering phenomenon.[3] At that time, the treatment for what he called "syndrome X" was thought to be lifestyle modification. Since 1988, there has been a flurry of research corroborating the idea of a risk factor cluster mediated by insulin resistance,[4–7] describing it using factor analysis,[8–13] and linking it with CVD.[13–16]

A new thread in the story of the metabolic syndrome emerged at the turn of the millennium. Several groups, including the World Health Organization (WHO)[17] and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII),[18] published clinical definitions of the metabolic syndrome intended for use in assigning clinical diagnoses to patients. This was followed by creation of an *International Classification of Diseases* diagnostic code (277.7) for metabolic syndrome. Although these definitions provided some uniformity to research efforts over the past 5 years, they also changed the focus of the metabolic syndrome to the clinical setting. The current confusion about whether the term "metabolic syndrome" refers to pathophysiological observation or clinical diagnosis stems from this abrupt change in focus.

Confusion has led to a climate of skepticism about the future of the metabolic syndrome. Is it an artificial, mathematical concept that simply recasts old known risk factors into a new disease entity?[19] Or does the clustering indeed reflect a single pathophysiology that can be a target for therapeutic decisions?[20,21] Can the metabolic syndrome offer advantages over existing models for the prediction of cardiovascular events?[22] Or given the confusion and the lingering doubts about its potential role in clinical practice, should the metabolic syndrome simply be declared dead?[23] Although these are all defensible concerns, the current conflict over the metabolic syndrome is still largely about differences in its intended function. The trouble remains ambiguity about what the metabolic syndrome is, how it should be defined, and what the purpose is for its existence.

Given the confusion over the metabolic syndrome, we sought to make explicit the present usage of the term in the literature and to suggest a framework for organizing its many descriptions.

IN BRIEF

The term "metabolic syndrome" refers to a cluster of risk factors for cardiovascular disease and type 2 diabetes that occurs as a result of obesity and insulin resistance. Considerable confusion surrounding the precise use of this term in the clinical setting has led to difficulty in assessing the utility of this concept. This article provides a simple framework for understanding the disparate approaches to this syndrome. This understanding will facilitate decision-making regarding the role of the metabolic syndrome in everyday clinical practice.

Methods

We searched the National Library of Medicine's Medline database for human studies published since 1988, using combinations of the following text words in their titles or abstracts: "metabolic syndrome," "definition," "insulin resistance syndrome," "dysmetabolic syndrome," and "syndrome X." The search was augmented by scanning selected journals through March 2006. Bibliographies of all retrieved articles served as a check of the completeness of the electronic search.

After screening the titles of the 4,544 identified articles, we examined

abstracts of 1,620 articles available in English for pertinence to the study objective. Full text was examined of 442 articles incorporating explicit use of the metabolic syndrome as either a study exposure or an outcome. Studies referring to a different metabolic syndrome (e.g., microvascular angina syndromes) and studies lacking a clear definition of the metabolic syndrome were excluded.

The descriptions of the metabolic syndrome used in the selected studies were abstracted, and the articles were grouped by their approach to defining the syndrome.

Table 1. Pathophysiological Changes Associated With Insulin Resistance

Atherogenic Dyslipidemia
- Increased triglycerides, apolipoprotein B
- Increased postprandial lipemia
- Decreased HDL, LDL particle size

Hypertension
- Increased sympathetic tone
- Increased renal Na^+ retention

Impaired Glycemia
- Impaired fasting glucose
- Impaired glucose tolerance

Proinflammatory State/Endothelial Dysfunction
- Increased C-reactive protein, white blood cell count
- Increased cytokines (IL-6, TNF-α, etc.)
- Increased mononuclear adhesion
- Microaluminuria

Prothrombotic State
- Increased plasminogen activator inhibitor-1
- Increased fibrinogen

Disordered Adipose Metabolism
- Elevated nonesterified free fatty acids
- Elevated adipokines (TNF-α, IL-6, leptin, resistin)
- Decreased adiponectin

Increased Liver Fat Content

Abnormal Uric Acid Metabolism

Abnormal Ovarian Androgen Secretion

Adapted from Ref. 24. IL, interleukin; TNG, tumor necrosis factor.

Pathophysiological Perspective

The pathophysiological perspective seeks to demonstrate how a single defect, insulin resistance, leads to a variety of pathological changes (Table 1), resulting in increased risk for a constellation of clinical conditions (Table 2).[24] It should be noted that CVD is just one of these important clinical conditions. Whereas the outdated term "syndrome X" focused only on CVD, we now understand that insulin resistance is mechanistically implicated in the development of polycystic ovarian syndrome (PCOS), nonalcoholic fatty liver disease (NAFLD), breast cancer, and other conditions. In this way, the intent of the metabolic syndrome is to provide a conceptual framework for understanding why clinical conditions cluster in individual patients. In short, it explains to practitioners why an obese, insulin-resistant individual is likely to have elevated liver transaminases (NAFLD), irregular menstrual cycles (PCOS), and a proinflammatory state manifested by elevated C-reactive protein and be at risk for developing several types of cancer.

From the pathophysiological perspective, the blame for the syndrome rests squarely on insulin resistance and the resultant hyperinsulinemia. This view is supported by evidence from the basic science and clinical research laboratories from the past 30 years.[3,24] Obesity is thought to exacerbate insulin resistance and thus increase the likelihood of an associated adverse clinical condition, but it is not considered a fundamental component of the syndrome because it need not be present. Proponents defend this decision with data showing that insulin resistance is indeed not a cause of obesity[24] and that the clustering of risk factors can occur in insulin-resistant individuals of normal weight.[25] Most of those approaching the metabolic syndrome from this perspective, particularly basic scientists and endocrinologists, prefer the term "insulin resistance syndrome" to stress the underlying pathophysiology.

The primary goal of the metabolic syndrome from the pathophysiological perspective is to alert physicians to an increased likelihood of multiple adverse conditions in insulin-resistant patients. Making a clinical diagnosis of metabolic syndrome based on strict criteria is not the focus, nor is using the syndrome as a cardiovascular risk calculator. From this perspective, the prevalence of metabolic syndrome can simply be defined by the distribution of insulin sensitivity in the population. Approximately one-third of the apparently healthy population is sufficiently insulin resistant to be at increased risk for the abnormalities shown in Table 2.[26] The current treatment for these individuals is considered to be lifestyle modification for the improvement of insulin sensitivity.

Clinical Epidemiological Perspective

The clinical epidemiological perspective seeks to assemble a group of

Table 2. Clinical Conditions Associated With Insulin Resistance

Type 2 diabetes
Cardiovascular disease
Essential hypertension
Polycystic ovarian syndrome
Nonalcoholic fatty liver disease
Gallstone disease
Cancer (i.e., breast cancer)
Sleep apnea

Adapted from Ref. 24.

related metabolic risk factors and to use this grouping for the prediction of future cardiovascular events. Decisions about which risk factors comprise the metabolic syndrome and their threshold values are based largely on their predictive values, with less emphasis on a unifying pathophysiological entity. Thus, from this perspective, obesity is considered a core component of the metabolic syndrome rather than a modulator of the effects of insulin resistance.[27]

The primary clinical goals of this approach are to make a diagnosis of metabolic syndrome and to use this diagnosis for risk stratification of patients according to their long-term likelihood (> 10–30 years) for atherosclerotic CVD.[28,29] The metabolic syndrome is not designed to be a competitor to the Framingham risk score, which calculates short-term risk over the course of 10 years.[30] Rather, it is formulated to aid the global assessment of lifetime risk. Generally speaking, advocates of this approach to the metabolic syndrome include lipid specialists and cardiologists. First-line treatment for metabolic syndrome is once again lifestyle intervention, with particular attention to dyslipidemia.[18,29]

Advocates of this approach support their formulations of the metabolic syndrome with data from population-based epidemiological studies.[13,16,31–40] Frequently, these are post hoc analyses of large prospective cohort studies or clinical trials. In general, these studies support the idea that a cluster of metabolic risk factors can predict cardiovascular outcomes better than the sum of its component risk variables considered individually.[41] For example, Isomaa et al.[16] found a threefold increased risk of coronary heart disease and stroke with the metabolic syndrome in the Botnia study, and Lakka et al.[13] reported a relative risk of 4.2 for death from coronary heart disease after adjusting for known risk factors in the Kuopio Ischaemic Heart Disease Risk Factor Study. However, few cohorts have been assembled with the primary intent of studying the metabolic syndrome.

Differences in the Perspectives

These two approaches to the metabolic syndrome are fundamentally different. (Table 3.) The pathophysiological perspective begins with a single defect, insulin resistance, and explores its consequences. CVD is just one of these consequences. The clinical epidemiological perspective is concerned primarily with CVD and the construction of a set of risk factors that best predict cardiovascular outcomes. From this perspective, insulin resistance may or may not explain the clustering phenomenon relating the risk factors; the pathophysiological mechanism is less immediate.

These two approaches can perhaps be better understood with a simple analogy. In many ways, the difference between the goals of the pathophysiological and clinical epidemiological perspectives is analogous to the differences between an exploratory prospective study and a retrospective case-control study (Figure 1). In a prospective study, a single exposure is defined, with the goal of measuring a set of outcomes that might be associated with that exposure. In a similar way, the pathophysiological perspective seeks to begin with a single exposure, insulin resistance, and explain how it leads to variety of clinical conditions (PCOS, NAFLD, and CVD, for example). In a case-control study, a single outcome is defined, and the goal of the study is to construct a set of risk factors for that outcome. In a similar way, the clinical epidemiological perspective begins with a single outcome, CVD, and attempts to describe a set of correlated risk factors for the prediction of CVD.

There are several implications of this difference in approach. Foremost is the impact on our understanding of the role of obesity in the metabolic syndrome. From the clinical epidemiological perspective, obesity is thought to play the central role because it best explains the occurrence of the other syndrome components, and in many studies it is the individual component most predictive of CVD.[42–44] From this perspective, the metabolic syndrome epidemic

Table 3. Comparison of the Two Approaches to the Metabolic Syndrome

	Pathophysiological	Clinical Epidemiological
Term	Insulin resistance syndrome	Metabolic syndrome
Purpose	Provide a conceptual framework for understanding clustering of risk factors and other adverse clinical conditions	Predict CVD based on presence of risk factor cluster
Clinical Goals	Alert physicians that patients with insulin resistance are at risk for multiple adverse clinical conditions	1. Make clinical diagnoses 2. Risk-stratify patients 3. Guide treatment decisions
Seeks Strict Clinical Definition?	No	Yes
Available Definitions	AACE	WHO, NCEP ATPIII, IDF
Advocates	Endocrinologists	Lipidologists, cardiologists
Research Tools	Basic science, clinical research laboratories	Population-based studies

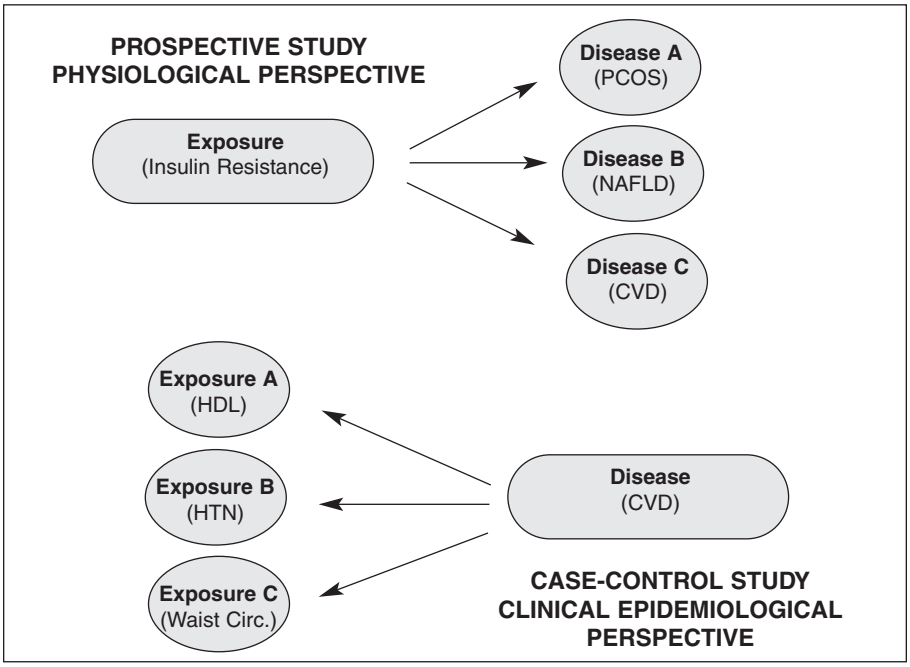

Figure 1. Visualization of the difference between the two approaches to the metabolic syndrome with analogy to common study designs. HTN, hypertension; Waist Circ, waist circumference.

has resulted from an obesity epidemic, and reducing patient weight is therefore viewed as a goal of therapy. From the pathophysiological perspective, obesity plays a peripheral role in the metabolic syndrome. Adiposity is considered a modest contributor to the metabolic syndrome, explaining about as much of the variation in the syndrome as physical fitness (~ 25%), considerably less than that contributed by genetic predispositions to insulin resistance.[45] Proponents argue that it is insulin-resistant obese people, not insulin-sensitive ones, who suffer from increased rates of the diseases associated with the metabolic syndrome.[46] To quote Gerald Reaven, "All obese people are not created equal—insulin resistance is the major determinant of cardiovascular disease in overweight/obese individuals."[46] Obesity is considered simply a modulator of the underlying disease.

Second is the issue of other diseases related to insulin resistance. Are they are a part of the metabolic syndrome? From the pathophysiological perspective, conditions such as PCOS and NAFLD are a crucial part of the clinical picture of the insulin-resistant patient. However, they currently have little role in the clinical epidemiological perspective and thus in most current clinical definitions because they are not well-studied risk factors for CVD.

Finally, the difference in approach has implications for the inclusion of new components in clinical metabolic syndrome definitions. For example, some have criticized the predictive power of the metabolic syndrome relative to the Framingham risk equation and suggested the inclusion of age, sex, or smoking in the syndrome.[22] Although these risk factors would certainly improve the syndrome's predictive power, they certainly are not consequences of insulin resistance.[24] Proponents of the pathophysiological perspective would thus reject their inclusion. However, these same scientists may argue for the inclusion of adiponectin, which is highly correlated with insulin resistance, yet is not as well studied as a predictor of cardiovascular events.[47,48] On the other hand, a risk factor such as C-reactive protein appears both to offer improved predictive power and to be a consequence of insulin resistance and thus is championed by scientists from both perspectives.[49]

Current Definitions

The WHO "working definition" published in 1998 and revised in 1999 was the first available clinical definition.[17] This definition recognized CVD as the primary outcome of the syndrome and suggested that whereas "each component of the cluster conveys [cardiovascular] risk . . . as a combination they become much more powerful."[17] This document recommended "vigorous early management of the syndrome"[17] for the prevention of adverse cardiovascular events. Emphasis was placed on detection of insulin resistance, requiring either a direct or indirect measure of insulin sensitivity for diagnosis. The remaining criteria, two of which must be present, include elevated blood pressure, elevated triglycerides, reduced HDL, and central obesity.

The NCEP ATPIII proposed a simpler, easier-to-use definition in 2001[18] and revised it in 2005.[29] The purpose of this definition was "to identify people at higher long-term risk for atherosclerotic cardiovascular disease" and target them for "clinical management of obesity and its metabolic complications."[29] At least three of five well-known cardiovascular risk factors must be present for diagnosis. Emphasis is placed on abdominal obesity as measured by waist circumference rather than an explicit requirement for insulin resistance. In general, the NCEP ATPIII definition requires less abnormality in the risk variables than the WHO definition. The NCEP ATPIII noted that, with regard to etiology, "no single pathogenesis has been elucidated, nor may one exist."[29]

In 2003, the American Academy of Clinical Endocrinologists (AACE) proposed criteria for an "insulin resistance syndrome."[50] AACE chose this term to refocus the discussion on the underlying pathogenesis of insulin resistance and resultant hyperinsulinemia. This definition, drawing largely from the pathophysiological perspective, is much

broader and includes noncardiovascular consequences of insulin resistance, such as NAFLD and PCOS. A family history of type 2 diabetes is also considered a risk factor for the syndrome. Most strikingly, there is no set number of criteria necessary for diagnosis; AACE considers this a matter to be determined by physicians. Thus, the purpose of the AACE definition is to alert physicians to the underlying metabolic state of patients, rather than to indicate a particular level of cardiovascular risk. A comparison of these definitions is shown in Table 4.

The International Diabetes Federation (IDF) definition, proposed in 2005, is the most recent entry into the competition to define the metabolic syndrome.[44] It nearly reiterates the NCEP ATPIII definition, yet it takes the emphasis on central obesity even further by requiring an enlarged waist circumference for diagnosis.

Remaining Questions

Which perspective best represents the metabolic syndrome? Should the focus be on the pathophysiology of insulin resistance and its consequences? Or should the focus be on the use of risk factor clusters to predict cardiovascular events? Answers to these questions will determine how we assess the utility of the syndrome in our clinical practices and how we approach proposed clinical definitions such as those of the WHO and the NCEP ATPIII.

From the pathophysiological perspective, clinicians should critically evaluate the following questions:

1. Do insulin resistance and the resultant compensatory hyperinsulinemia adequately explain the risk factor clustering?
2. Do current clinical definitions adequately identify individuals who are insulin resistant?
3. Can insulin resistance be treated?
4. Can the complications of insulin resistance/hyperinsulinemia be prevented?

From the clinical epidemiological perspective, we must ask:

1. Does the metabolic syndrome predict cardiovascular events better than its component risk factors?
2. Why are certain risk factors for CVD included in the definition, whereas others are not (e.g., C-reactive protein)?[51]
3. Why dichotomize risk variables with a binary metabolic syndrome definition when a risk equation with continuous measures would better express overall risk?
4. Are all patients with metabolic syndrome at similar risk, or is it in fact a more heterogeneous group?
5. Does the treatment for metabolic syndrome differ from the common treatment of its individual component risk factors?

These questions have been reviewed in detail elsewhere.[21] By organizing them according to perspective (pathophysiological versus clinical epidemiological), we hope to help clinicians focus their evaluation of metabolic syndrome based on explicit expecta-

Table 4. Comparison of the Current Clinical Definitions of the Metabolic Syndrome

WHO	NCEP ATPIII	AACE
Insulin resistance identified as either: • Type 2 diabetes • Impaired fasting glucose • Impaired glucose tolerance • As determined by hyperinsulinemic, euglycemic clamp Plus any two of the following: • Hypertension (≥ 140/90 mmHg) • Plasma triglycerides ≥ 150 mg/dl or HDL cholesterol < 35 mg/dl in men or < 39 mg/dl in women • BMI > 30 kg/m^2 and/or waist-to-hip ratio of > 0.9 inches in men or > 0.85 inches in women • Microalbuminuria	At least three of the following five criteria: • Waist circumference: Men ≥ 102 cm (≥ 40 inches) Women ≥ 88 cm (≥ 35 inches) • Triglycerides ≥ 150 mg/dl • HDL cholesterol Men < 40 mg/dl Women < 50 mg/dl • Hypertension ≥ 130/85 mmHg or antihypertensive medication • Fasting glucose ≥ 100 mg/dl	• 2-hour post–glucose challenge >140 mg/dl • Fasting glucose 110–126 mg/dl • BMI ≥ 25 kg/m^2 • Triglycerides ≥ 150 mg/dl • HDL cholesterol: Men < 40 mg/dl Women < 50 mg/dl • Hypertension ≥ 130/85 mmHg Other related factors • Family history of type 2 diabetes, hypertension, or CVD • PCOS • Sedentary lifestyle • High-risk ethnic groups • NAFLD • Acanthosis nigricans • Pediatric modifications of risk-variable thresholds

tions of the concept in their own clinical practices.

Clinical Utility

During the past year, both the American Diabetes Association (ADA)[21] and the American Heart Association (AHA)[28] have published position statements on the metabolic syndrome. The ADA, leaning toward the pathophysiological perspective, cites imprecise definition of the syndrome, lack of certainty over its pathogenesis, and doubt about its use as a single CVD risk marker in its decision to not support clinical use of the metabolic syndrome. At the very least, the ADA prefers that patients with type 2 diabetes not be eligible for diagnosis. The ADA appears frustrated with the present trajectory of the metabolic syndrome, stating that the supporters of the syndrome "focus on the syndrome and don't concentrate on the disease."[21]

In sharp contrast, the AHA stands behind the NCEP ATPIII definition of the metabolic syndrome. While admitting its imperfections, the AHA argues that the diagnostic criteria are in evolution and that the syndrome represents a significant step forward in the holistic treatment of the commonly overlooked cardiovascular risk factors seen in obese patients. This organization is less troubled by a unifying pathogenesis, stating that the syndrome probably has more than one cause. "Regardless of cause," the AHA statement notes, "the syndrome identifies individuals at elevated risk for atherosclerotic cardiovascular disease."[28]

Scott Grundy, a lipidologist and champion of the NCEP ATPIII definition, has recently published an article titled "Metabolic Syndrome: Connecting and Reconciling Cardiovascular and Diabetes Worlds."[41] Indeed, a growing number of clinicians are noticing the divergence between the diabetes and cardiology communities. Others simply conclude that, given the seemingly arbitrary clinical definitions and the uncertain clinical utility, the metabolic syndrome should be declared dead.[23] Who is right? The answer depends, as usual, on your perspective.

Perspectives are rarely changed by another review article. Events, not words, change perspectives. The most likely event that would bridge these differences, if not render them moot, would be the development of new products that either target an underlying unifying pathophysiological process or a system that modulates that process. Several possibilities, ranging from the thiazolidinedione-like class peroxisome proliferator–activated receptor-δ,γ agonists targeting insulin resistance[52,53] to newer agents selectively targeting the endocannabinoid system,[54,55] may bring some resolution to this debate. They may, that is, if they prove safe and effective in treating individuals with an agreed-upon cluster of findings.

In the meantime, physicians must be clear what they mean by "metabolic syndrome." With more precise usage of this term, we might make focused criticisms of the current clinical definitions of the syndrome and make informed decisions about the usefulness of the metabolic syndrome concept in our own clinical practices.

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