Metabolic Syndrome
A Work in Progress, but a Useful Construct
Richard S. Beaser, MD; Philip Levy, MD

The metabolic syndrome is a construct that has come into common usage over the last few decades. In 1956, Jean Vague first demonstrated that upper-body obesity determined predisposition to diabetes mellitus, atherosclerosis, gout, and renal calculi; however, it was the presentation of this concept by Gerald Reaven in his Banting Lecture in 1988 that initiated the current focus on this entity as a clinical and pathological construct. Dr Reaven suggested that 3 major conditions—non–insulin-dependent diabetes mellitus (type 2 diabetes mellitus), hypertension, and coronary artery disease—had an causal commonality (resistance to insulin-stimulated glucose uptake and hyperinsulinemia) and referred to this constellation of abnormalities as “syndrome X.” He did not include abdominal obesity in the original description, nor did he comment significantly on a potential clinical role for his observations. In fact, his concluding sentences stated, “What remains to be seen is the magnitude of the role that resistance to insulin-stimulated glucose uptake plays in the etiology of human disease. I can only hope that this presentation has outlined the possibilities for future efforts to answer this question.”

Response by Kahn p 1818

Since that time, this construct has evolved conceptually and functionally into an entity that many refer to as a “syndrome.” More recently, there have been many questions about the legitimacy of this designation, summarized by Kahn et al in a September 2005 position statement for the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Their comments called into question many of the assumptions that underlay the designation of “syndrome,” and they posed the following key questions: How clear is the existing definition of the metabolic syndrome for diagnostic purposes? How useful is the syndrome definition in predicting cardiovascular disease (CVD) risk? Do the individual components of the syndrome convey “risk” differently from the syndrome as a whole? Is the cluster of symptoms associated with the syndrome the result of a common underlying pathological process? Does the treatment of the metabolic syndrome differ from the treatment of its individual components? What additional work should be done to improve our current knowledge of the metabolic syndrome?

This opening salvo started an ongoing volley of commentary on the legitimacy of this construct as a syndrome. Our intent in this article is to present a practical, clinician’s perspective and a challenge for the cardiology and diabetes communities to refine this entity into a useful tool.

What Is It? Or Perhaps a Better Question, Why Is It?

Before delving into discussions of what this construct or constellation of associations may be, it is probably best to start from the clinician’s perspective: Why is it? What utility does it have, or do we want it to have, in clinical care?
The ADA/EASD report suggested that the purpose of the construct is to predict CVD. They did not evaluate papers or analyses that used the syndrome to predict diabetes mellitus, because the syndrome already includes glucose intolerance. We concur. Further more useful would be a means of identifying what may be earlier markers of CVD and using them to stratify subsequent risk of an undesirable outcome. Hence, we agree with the authors that the greatest utility would come from an ability to predict CVD.

Next, to further set the limits of this discussion, we looked at the definition of the word “syndrome.” Merriam-Webster’s definition is “a group of signs and symptoms that occur together and characterize a particular abnormality or condition; a set of concurrent things (as emotions or actions) that usually form an identifiable pattern.” A more medically focused view should be provided by Stedman’s online medical dictionary, which defines “syndrome” as “The aggregate of symptoms and signs associated with any morbid process, and factors such as inactivity, age, other endocrine issues, and genetics that can exacerbate the impact, arguing that “a multifactorial etiology does not negate the syndrome’s existence.” Thus, trying to confine the syndrome to a limited number of specific, fixed parameters for all populations may be simplistic owing to the heterogeneity among various populations.

The definition of “syndrome” pervaded much of the discussion that appeared in the medical literature in the last year and is the underpinning of the concerns. Does the sum have to be greater than the parts? Does there have to be a common origin? Or can it provide a functional construct without these characteristics? Ultimately, this argument will be debated as long as there are physicians, because these issues can be applied to many situations in medicine. However, let us explore the key elements of the argument as it applies to the metabolic syndrome.

**Is There One Underlying Pathophysiology?**

Intuitively, many people believe there is; however, as noted above, it appears evident that the pathophysiology may have genetic differences and variations in clinical manifestations, which makes a clear definition and identification more difficult. Certainly, studies such as the Heart Outcomes Prevention Evaluation (HOPE) trial, in which an angiotensin-converting enzyme (ACE) inhibitor impacted the development of diabetes mellitus, and the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication study (DREAM), in which an ACE inhibitor similarly impacted glucose levels, suggest some causal commonality.

Specific arguments in favor of a single underlying origin were also put forth in response to the ADA/EASD position statement. Pladevall et al reported the use of confirmatory factor analysis to test the hypothesis that the components of the metabolic syndrome are manifestations of a single common factor. Using a 1-factor model with the key metabolic syndrome components of waist circumference, insulin resistance, mean arterial blood pressure, and triglyceride-to-high-density lipoprotein ratio, they argued that the current model does have a single origin of insulin resistance and noted the link between abdominal obesity and insulin resistance. They argued that the concept of a single underlying causative factor is plausible and is the best explanation for the correlations among the core metabolic syndrome components, which occur with a frequency greater than would be expected by chance, making the metabolic syndrome a distinct entity.

Reaven also underscored the likelihood that the underlying process is insulin resistance. Yet many, including the International Diabetes Federation, argued that the factor is obesity. The issue remains, of course, that in the clinical arena, direct measurement of insulin resistance is not practical, and many assume that obesity is a useful surrogate. However, it does not have a 100% correlation, because many thinner or only slightly overweight people with the metabolic syndrome exist, and many obese people are without it. Yet, the focus on abdominal obesity does seem to be promising and introduces the possible roles of adipose tissue and substances associated with it. Furthermore, some of the inconsistencies seen in the association of abdominal obesity and insulin resistance and/or increased cardiac risk may be a reflection of methods of measurement, such as body mass index (which is a poor measure of abdominal adiposity).
or waist circumference (which is better but not perfect). Ultrasound measurements of intraabdominal fat may be a better metric, although not as convenient in a busy practice setting. We believe cogent arguments exist for obesity being an important focus of the ongoing efforts to further clarify and refine the definition of this syndrome, because its causative role and utility as a marker appear to be quite promising clinically.

Is the Risk of the Syndrome More Than the Sum of the Parts, and Implicit in This, Do We Have the Correct Defining Components?

In putting forth the argument that the unifying pathophysiology has not yet been properly identified, the ADA/EASD position paper points out inconsistencies in measurements of insulin resistance and in the relationship between insulin resistance and hyperinsulinemia. It states that other unidentified factors may potentially play key roles; components that may be related to insulin resistance only loosely and others that are clearly related (such as C-reactive protein and adiponectin) are excluded.

Yet, others demonstrated that the current definitions do predict risk. Ninomiya et al examined the association of the metabolic syndrome by National Cholesterol Education Program definition with a history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey (NHANES III) and found that there was a strong, consistent relationship. Meigs et al found that among nondiabetic subjects from the Framingham Offspring Study, a clustering of risk factors, including hyperinsulinemia, dyslipidemia, hypertension, and glucose intolerance (rather than hyperinsulinemia alone), characterized the underlying features of the insulin resistance syndrome.

Eberly et al., reporting from the MRFIT group, noted that not only was the metabolic syndrome associated with an increased risk of mortality, but there was a further additive increase with 3 metabolic syndrome conditions or when accompanied by additional factors, such as cigarette smoking or elevated LDL cholesterol. Although confirming that the current definition does reflect increased risk, the authors questioned whether this particular clustering and means of defining the syndrome was optimal. The INTERHEART study also demonstrated that increasing numbers of risk factors result in a multiplicative increase in atherosclerotic cardiovascular disease risk, yet the many factors examined in that study do underscore the question of whether the specific metabolic syndrome factors are correct.

Grundy supports the perspective that if insulin resistance is the underlying causative component, and the definition of type 2 diabetes mellitus is hyperglycemia caused by the dual defects of insulin resistance and insulin secretory deficiency, then type 2 diabetes mellitus would be an important component of this risk-conferring syndrome.

Overlap With Diagnosed Disease: Should This Be a Spectrum of Risk Rather Than “Present” Versus “Absent”?

Throughout the discussions of the definition of the metabolic syndrome, the dominant question is what degree of abnormality should be used to qualify a risk factor for inclusion. Should we consider a spectrum of risk based on a varying numeric measure of a risk factor rather than an all-or-nothing risk stratification? Furthermore, once one qualifies for a “disease” such as diabetes mellitus, would that in and of itself increase CVD risk that those with the diagnosis should be excluded from the group labeled with the metabolic syndrome? If we look at this construct as trying to identify people with “borderline” parameters to determine whether the sum of these parameters increases risk, then the argument would be that once diabetes mellitus is diagnosed, patients are already in an increased risk category and the metabolic syndrome is no longer needed to increase the level of clinical concern.

Many argue that those with diabetes mellitus should be considered part of the metabolic syndrome spectrum. Grundy supports the perspective that if insulin resistance is the underlying causative component, and the definition of type 2 diabetes mellitus is hyperglycemia caused by the dual defects of insulin resistance and insulin secretory deficiency, then type 2 diabetes mellitus would be an important component of this risk-conferring syndrome.

Alexander et al sought to quantify the increased prevalence of coronary heart disease among people with metabolic syndrome. They used NHANES III to categorize adults over 50 years of age with or without diabetes mellitus by the presence of metabolic syndrome per the National Cholesterol Education Program definition. They reported that the prevalence of coronary heart disease markedly increases with the presence of metabolic syndrome. In addition, the prevalence of coronary heart disease among people with diabetes mellitus was increased compared with the prevalence among those with metabolic syndrome without diabetes. However, individuals with diabetes without metabolic syndrome had approximately the same prevalence of coronary heart disease as those with neither. Implicit in this finding is the fact that even if the definition of type 2 diabetes mellitus should be a surrogate for insulin resistance, without other manifestations of the syndrome, it is not necessarily a reflection of increased CVD risk. Thus, in and of itself, it is not an adequate marker, and conversely, it is a useful component of the metabolic syndrome.

What about prediabetes: glucose intolerance that does not meet diabetes diagnostic criteria? Hunt et al reported that...
prediabetes, manifested by impaired fasting glucose, is associated with CVD and all-cause mortality in the general population to a degree comparable to the metabolic syndrome or any of its components. In addition, the authors suggest that the National Cholesterol Education Program definition of the metabolic syndrome was more predictive of CVD in the lower-risk populations. These data were used by the ADA/EASD authors to argue that the presence of diabetes mellitus overwhelms the other components, whereas Grundy commented that impaired fasting glucose may still not be a strong enough predictor by itself. Others also suggested that risk factors on the lower end of the scales of measurement may not confer as much risk. Certainly, this discussion harkens back to the previous concern about whether we really have the correct components, and the answer to the question of “mild” versus “moderate” abnormalities may become more evident when applied to other components, perhaps some more closely related to abdominal obesity.

A key question relating to this discussion is whether preventive interventions for prediabetes with medications such as thiazolidinediones, or even ACE inhibitors, will prevent CVD and metabolic risk factors. In fact, since that publication, the results of the DREAM trial failed to demonstrate that treatment to improve insulin sensitivity in people with impaired glucose tolerance prevented cardiovascular events, although it did affect progression to frank diabetes mellitus. In addition, the results of the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROActive) study were unimpressive in CVD prevention in those who already had established disease. For these reasons, the ADA/EASD position was that the metabolic syndrome should not, by itself, be a treatment target.

Grundy countered that clinical benefits of identifying this syndrome do exist. He argued that identifying the syndrome helps to direct care toward lifestyle and a coordinated effort at reducing all of the key risk factors. It identifies people who would benefit from a more “refined” risk analysis, such as the Framingham risk score or glucose tolerance testing. It also stimulates more aggressive long-term follow-up with ongoing lifestyle interventions, and on the basis of the more detailed risk analysis, consideration of the use of risk-reducing drugs that target individual risk factors.

Yet, the counterargument put forth in the ADA/EASD position statement is that we should not need the syndrome label and that treatment of the individual risk factors should occur on the basis of their mere presence. However, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology responded to this argument. They reviewed the American College of Endocrinology 2003 statement on the insulin resistance syndrome, which focused specifically on insulin resistance and its association with a number of disease consequences. They also pointed out that insulin resistance may play a role in infertility, fatty liver, some malignancies, and degenerative central nervous system disease. Their position was that this concept serves to predict, and lead to prevention of, such consequences, because resistance to insulin is a major driver of atherosclerosis and diabetes mellitus.

The American College of Endocrinology/AACE group argued that the metabolic syndrome is a useful tool to assist clinicians in recognizing the cluster of factors that increase the risk of insulin resistance. This perspective is supported by unpublished internal evaluation data from the educational impact assessments conducted by the Joslin Professional Education Department after multiple continuing medical education programs identified in the title by the term “metabolic syndrome” (Enrique Caballero, MD, and Richard Beaser, MD, unpublished data, 2006).

In a pretest based on a case vignette assessment tool, 71% of attendees recognized the constellation of risk markers that constitute the metabolic syndrome. Similarly, 68% of a control group of physicians who did not attend this program but who had attended previous programs recognized the constellation. We emphasize that this was before any educational intervention. Although there were self-selected physicians who attended an educational program that focused on the metabolic syndrome, comparable numbers were seen among the control group, physicians interested in diabetes treatment issues who chose not to attend this educational activity. We interpret these data to suggest that knowledge of the components of the metabolic syndrome is a known focal point for many physicians already interested in diabetes mellitus and metabolic risk for identification of patients at risk. It may also draw some physicians in to educational activities. Whether or not the same level of focus would have occurred had the syndrome not been identified is unclear; however, the description appears to be a useful clinical tool for many physicians.
Clinical experience demonstrates that some patients also find the identification of this clustering as a syndrome to be useful because it provides a simple construct for them to address. Recognizing that each patient may respond differently, the physician must have multiple approaches ready and must apply whichever one it is believed the patient will best respond to. For one patient, telling him that he has hypertension, elevated lipids, obesity, and elevated glucose may challenge him to address these many issues, but to another, it may be an overwhelming array of diagnoses that may seem insurmountable. That second patient may feel better with a single umbrella diagnosis of the metabolic syndrome, with various nonpharmacological and pharmacological treatments available to treat it. This unified approach to therapy through the recognition of a cluster of cardiovascular risk factors can also stimulate a search for other disorders that are associated with the syndrome. For didactic and practical purposes, the term “syndrome” is conceptually attractive and clinically useful, providing a simple construct to describe a patient type that clinicians see daily.

The previously described American College of Endocrinology/AACE position35 notes that these groups were instrumental in obtaining the International Classification of Diseases–9th Revision (ICD-9) code 277.7 (dysmetabolic syndrome X). This coding legitimizes the medical necessity of testing for related risk factors when aspects of this syndrome are present. The American College of Endocrinology and the AACE developed their original position statement on the basis of published scientific literature. The present authors, as well as the American College of Endocrinology and the AACE, encourage further research into this field, as well as a standardized insulin assay. The American College of Endocrinology and the AACE believe that the concept of insulin resistance as a syndrome has been helpful to both clinicians and patients.

The American College of Endocrinology/AACE position raises the issue of the financial implications inherent in whether or not we treat a syndrome versus its components. Payers typically differentiate support for treatment of disease from prevention, and thus the designation of the metabolic syndrome a disease versus addressing individual risk factors may impact multiple risk factors. Through this work, we come to grips with this disease from a scientific, sociological, and economic perspective regardless of label.

Comments and Conclusions

We have presented a summary of the arguments, pro and con, citing only a representation of the many hundreds of articles that have been published on this issue. Our perspective is that of diabetologists, physicians who also often educate primary care providers, and specialists who provide clinical care for this population.

It is our opinion that the metabolic syndrome is still a work in progress, and like any such concepts under construction, it may not be completed and ready for full use. Like a partially constructed boat, it may float, but it is not yet fully seaworthy. Still, we believe that it has utility—to some, in its current state, from a clinical perspective, and for others, as a stimulus to further refine its definition. Clearly, enough data exist to suggest the possible existence of a metabolic syndrome to continue efforts at its refinement. Too many treatments for 1 component of the spectrum of risk-conferring factors impact other clinical manifestations to discard the postulate that 1 or many common causative factors exist that may eventually become important clinical targets. Too much evidence exists to suggest that the sum may be greater than the parts to cease efforts to find the optimal mix of clinically measurable components to use in identifying individuals who need greater clinical attention. Having the syndrome and, yes, stimulating this storm of pro and con discussion that tests the validity of the concept will foster efforts to complete the construction of this concept into a more precise clinical entity.

The authors agree in principle with the ADA/EASD’s listing of areas for further clarification and put forth our perspective on them as follows:

- Which factors are optimal for inclusion in the syndrome, from the perspectives of their causes and clinical utility for identifying people with increased CVD risk? Would other factors such as C-reactive protein, family history, smoking, measurement of intra-abdominal adiposity or adipose-related substances, or gender add to the definition?
- Risk factors should be stratified with respect to their relative importance.
- Consideration should be given to the measurement of variables in terms of degrees of risk or upper and lower cut points rather than “all or nothing.” Furthermore, risk for some of the lesser-risk profiles should be stratified and clarified. The possibility of differing manifestations of these risk factors in various ethnic groups should be acknowledged.
- Aggressive investigation should take place to identify underlying causative commonalities of this cluster of CVD risk factors.
- The metabolic syndrome construct should be used to continue research and development into medications that may impact multiple risk factors. Through this work, we
may gain further insight into some of the common threads of this constellation of clinical markers.

Should a partial construct be used clinically? No one has argued that this does any harm and violates the Hippocratic Oath, the economic implications notwithstanding. However, for the clinician, here is where the science of medicine blends into the art. Many clinicians find it easier to present patients with a unified concept when addressing multiple treatment issues, and many patients may respond more effectively to such an imperfect but useful construct. Others may find it unnecessary. As long as there is no harm, we would argue to leave it up to the judgment of the clinician when dealing with each patient in trying to optimize adherence to therapy, while the academic community works to further refine the concept and more clearly make recommendations for treatment targets.

A key point, however, is that none of this discussion negates the need to address each risk factor individually. On the basis of data that reflect the impact of a particular factor on CVD risk and the benefits of resulting treatments, clinicians should not be reluctant to treat with aggressive non-pharmacological and pharmacological treatment just because a patient does not fit into the current metabolic syndrome profile. Furthermore, we should not limit treatment to only the components of the metabolic syndrome, but we should address any other factors known to increase CVD risk.

Thus, to paraphrase an old saying, a syndrome is in the eye of the beholder. It is a functional entity, and that function, on one level, may be to optimize the achievement of a clinical goal; on a deeper level, it may be to seek a pathophysiological truth that has eluded clear definition for the last few decades. Although its perceived utility to stimulate clinical care of and research into CVD risk may be debated, the goal toward which it is directed—optimization of patient care and outcomes—should not.

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Disclosures

Dr Beaser serves on the Academic Advisory Board for Keryx Biopharmaceuticals, Inc; Dr Levy serves on the Speakers’ Bureau for Amylin Pharmaceuticals, Inc; Bristol-Myers Squibb Co; GlaxoSmithKline; Eli Lilly & Co; Merck & Co, Inc; Novartis Pharmaceuticals Corporation; Novo Nordisk, Inc; Pfizer, Inc; and sanofi-aventis US and on the advisory boards of Eli Lilly & Co and Pfizer Inc; Dr Levy also receives clinical research support from Amylin Pharmaceuticals, Inc; MannKind Corporation; Novartis Pharmaceuticals Corp; Novo Nordisk, Inc; Pfizer, Inc; and sanofi-aventis US.

References

10. The DREAM (Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication) trial results. Paper presented at: 42nd Annual Meeting of the European Association for the Study of Diabetes (EASD); September 15, 2006; Copenhagen, Denmark.
Response to Beaser and Levy

Richard Kahn, PhD

The article by Beaser and Levy defends the utility of the metabolic syndrome by presenting an argument that is not supported by substantive evidence. In their section on pathophysiology, they cite 1 article in favor of a single underlying cause, but they fail to mention at least 10 others that provide evidence for multiple causes. The authors cite numerous articles in the section describing the risk being greater than the sum of its parts, but careful inspection of these articles reveals that none actually reached a conclusion supporting the authors’ claims; one, that by Yusuf et al (reference 24) appears to be an error because it did not discuss the metabolic syndrome. In their section arguing for the clinical utility of the syndrome, they cite editorial and a survey of attendees of a conference on the syndrome who appeared to know as much about the topic as a “control group.” Other evidence includes “clinical experience,” including testimonials from their colleagues and a successful lobbying effort by a trade organization to obtain an International Classification of Diseases code. The latter, they indicate, “has tremendous potential economic implications on reimbursement for treatments and the development and support of pharmaceutical agents.” Indeed, they seem to believe, “this issue may be the real root of this ongoing discussion.” Just exactly what is meant by that assertion is unclear, but surely they cannot mean that the innumerous articles refuting virtually all aspects of the syndrome as a beneficial clinical diagnosis should take a back seat to the economic interests of physicians and the pharmaceutical industry. In current times, when healthcare resources are strained and evidence-based medicine has become the foundation for medical practice, society might expect that in order for the medical community to establish a new disease (and the testing and “labeling” that comes with it), a rich body of scientific evidence would be in-hand to document some utility. Conversely, it seems inappropriate to rely on good intentions or to do what seems right “in the eye of the beholder” as the major justification for providers to seek to diagnose a condition called the metabolic syndrome.
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