The Metabolic Syndrome (Emperor) Wears No Clothes

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There are several key features of the metabolic syndrome that virtually all interested individuals and organizations agree upon. First, that certain "metabolic" factors tend to associate with each other more often than chance would dictate. Second, these risk factors taken alone or in any possible combination are associated with an elevated risk for cardiovascular disease (CVD) and diabetes. Third, there is no definitive treatment for the "syndrome" per se. Rather, therapy is individualized according to the degree to which any specific risk factor(s) is present in a patient, and everyone with any risk factor(s) should be given lifestyle modification counseling. Finally, despite over 10,000 articles on the subject, there is much missing information.

It is this last fact that has lead to the concern and consternation voiced by some organizations (1) and individuals (2–6). That is, the basic question is whether we know enough about this constellation of risk factors to warrant adopting a unique clinical construct that has value to either physicians or patients. After all, the fundamental purpose of a medical label (diagnosis) is to inform physicians and/or patients to take (or not take) action that would otherwise be different.

In this issue of *Diabetes Care* (7) and recently elsewhere (8), Scott Grundy, MD, PhD, perhaps the chief proponent of the syndrome as a clinical construct, defends its existence with a variety of arguments. Although he suggests the basic disagreement is one of "differences in perspectives and biases [between the] cardiovascular and diabetes communities" (7) and that it may boil down to "how to integrate the metabolic syndrome into concepts of insulin resistance, pre-diabetes, and type 2 diabetes" (8), in fact, the issues are much more fundamental, speak to the lack of a solid evidence base, and raise concerns that are critical to a core premise of a diagnostic label, i.e., its clinical utility.

What are the problems?

There is no biological basis for the diagnostic algorithm. One would have thought that any publication announcing a new or revised algorithm for diagnosing the metabolic syndrome would be accompanied by data describing *1*) the specific biological evidence that warrants the change and/or *2*) how the new/revised definition enhances the sensitivity, specificity, and positive predictive value of the diagnosis. Unfortunately, no such information has accompanied any article defining the syndrome (9–12). Moreover, it is doubtful that anyone has yet to explore the positive predictive value of defining the syndrome in the many ways it could be defined.

Worse yet, there has been no scientific evidence presented or cited, or even an explanation given, in any of the core syndrome reports, for why the algorithm is what it is. For example, why was three of five risk factors chosen to reach the diagnostic threshold? Why not one, two, four, or five of five factors? How about two mandatory (instead of one) and one/two optional? Which algorithm is better, and better for what end? If insulin resistance is at the core of the syndrome, why not include age (arguably the most powerful predictor of insulin resistance)? Of note, the fact that the metabolic syndrome, as defined, is a relatively insensitive indicator of insulin resistance (13–15) would seem to cast doubt on the fundamental premise that insulin resistance is optimally captured by the current definitions. And, if the syndrome includes or encompasses other "prothrombotic and proinflammatory states" or factors (8,10), why are there no such criteria in the definition?

There are other concerns that are not trivial. Why did the blood pressure criterion change from 130 and 85 mmHg (12) to 130 or 85 mmHg (9)? Since the change was not explained, it is possible that it was just an oversight or typographical error; however, if the change was intentional, did the authors appreciate that the latter definition will pick up substantially more individuals than the former definition? Also, why is the blood pressure cut point 130/85 mmHg instead of 135/80 or 125/75 mmHg?

It would seem that all of the above questions, as well as innumerable others, related to why the construct is defined as it is, would have already received much attention by the authors of the definitions, since we are dealing with a medical condition affecting tens of millions of people. By comparison, the justification for changing the cut point that defines diabetes was clearly documented and based on multiple studies in the literature (16).

The syndrome is a relatively poor predictor of future diabetes or CVD. There is no doubt that the presence of the syndrome is associated with a higher risk of diabetes or CVD. That fact is not surprising given that the definition includes two major risk factors for diabetes (i.e., obesity and glucose intolerance) and five risk factors for CVD. Yet, proponents of the syndrome repeatedly emphasize these predictive virtues as if a diagnosis of the syndrome now tells clinicians or patients something they otherwise would not know.

The more important question, of course, is what does the diagnosis tell us that other, simpler risk algorithms lack or that cannot be gleaned by simply noting the variables that define it (i.e., the parts)? Grundy (7) acknowledges that the Framingham score is a better "short-term" (10 year) risk tool, but he claims that the metabolic syndrome was meant to iden-

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Abbreviations: ATP, Adult Treatment Panel; CHD, coronary heart disease; CVD, cardiovascular disease; FPG, fasting plasma glucose.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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tify individuals at "higher long-term risk." Of note, however, none of his publications or that of the Adult Treatment Panel (ATP) III provide any evidence that the syndrome is better at long-term compared with short-term prediction. To the contrary, the vast majority of articles in the scientific literature showing an association between the syndrome and incident diabetes or CVD followed their cohorts for <10 years, and it's not obvious from the other studies, which followed populations for longer periods, that the predictive value of the diagnosis improved. Moreover, a recent study by Wannamethee et al. (17) showed that in a cohort followed for 20 years, the Framingham Risk Score was still a better CVD predictive tool than the metabolic syndrome.

Perhaps the argument could be made that Framingham is too cumbersome, and something better, easier, and with a more catchy name (like the metabolic syndrome) is a more practical risk prediction tool. But in response, one could cite the many reports (18–20) showing that a single, simple measure of blood glucose is a far better predictor of incident diabetes than the complex definition of the syndrome, which of course also requires both a measure of blood glucose and a lipid profile.

As for the syndrome's virtue to predict CVD more simply than other approaches, we have no data indicating that it is a better tool than measuring LDL cholesterol, which is already ingrained in the minds of clinicians, or that it is more predictive than simply noting a person's age, which is also a powerful prognostic indicator of CVD (and directly related to insulin resistance). But perhaps the diagnosis of the syndrome addresses the risk of CVD in ways independent of its parts? The recent study by Wilson et al. (20) seems to dispel even that notion, since they showed that the relative risk of CVD was essentially the same when the five metabolic syndrome factors were taken one, two, or even three at a time. In other words, if you want the simplest, cheapest, and seemingly most predictive way to determine the risk of diabetes and CVD in one fell swoop, just measure fasting plasma glucose (FPG).

It should be noted that since all of the syndrome variables have no upper cut-off limits, many individuals will be so diagnosed because they have frank diabetes, hypertension, or severe lipid abnormalities. Obviously, such individuals have a greatly elevated risk of CVD, and thus it's questionable what, if any, additional risk accrues due to having the "syndrome" versus a component(s) that is very elevated. It would be very informative to know the CVD risk in syndrome patients who only have borderline values (no frank disease), but no such study seems to have been published.

The question was nearly answered in the study by Vasan et al. (21), who examined the impact of a variety of CVD risk factors at borderline or elevated levels on the 10-year risk of coronary heart disease (CHD). Unfortunately, not all the risk factors included were components of the syndrome. Their study showed, however, that patients with one to four such borderline values (i.e., systolic blood pressure 120–139 mmHg, LDL cholesterol 100–159 mg/dl, HDL cholesterol 40–59 mg/dl, impaired fasting glucose 110–125 mg/dl, or impaired glucose tolerance 140–199 mg/dl or former smoker) and no markedly elevated risk factors accounted for a very small proportion of CHD events. Indeed, 90% of CHD events occurred in individuals with one or more elevated risk factor. Thus, their study lends evidence to the hypothesis that the CVD predictive value of the syndrome may not be so remarkable were it not for the fact that the definition sweeps up many patients who are at an unmistakably high risk. This discussion is not meant, of course, to imply that "borderline values" should be ignored, only that the utility of the metabolic syndrome label in such patients is untested.

The whole is not greater than the sum of the parts. Another key argument made in support of the syndrome is that the risk imparted by the condition is higher than the risk imparted by the component factors themselves. Grundy claims that this is true and that the risk factors are "multiplicative" (7), i.e., the whole is greater than the sum of its parts. Although that is not obvious in the one publication he cites (22), which seems only to address measurements of obesity and the risk of CVD, many other studies support the opposite conclusion. There are now at least seven studies showing that the risk of CVD associated with the syndrome is no greater than that explained by the presence of its components (20,23–29).

Although it may be true, as Grundy suggests (7), that the definition is confounded by "hidden" risk factors and its progressive worsening over time somehow speaks to the greater value of diagnosing the syndrome per se, there still remains the repeated observation that the adverse effects of the syndrome are expressed entirely by its components. Thus, we have yet to see any evidence that knowing a person has the syndrome provides more or better information to a clinician or patient than knowing if any of its components are apparent.

There is no scientific evidence that the syndrome has clinical utility. The primary argument against this criticism is that diagnosing the syndrome focuses attention on the need for lifestyle modification, and thus implicitly, such attention has value, i.e., weight loss and increased physical activity actually occur (7,8). Unfortunately, no data are cited (nor do any seem to exist) to support the hypothesis that telling someone they have metabolic syndrome results in more meaningful or longer-lasting behavior modification versus telling someone they have a variety of CVD risk factors. Since it's nearly gospel that for the vast majority of overweight/obese patients, weight loss is very difficult to maintain without regular professional support and counseling, it would seem remarkable that simply telling someone they have the metabolic syndrome is more effective.

Alternatively, when the perils of overweight/obesity have been the subject of endless news stories and a steady stream of scientific publications, do clinicians really need to diagnose the metabolic syndrome in order to stress the benefits of normal weight and regular exercise? But to be fair, and to Dr. Grundy's enormous credit as Chair of the ATP III panel, he recognized early on that the medical community seemed to be ignoring ATP II's emphasis on weight reduction as a critical component of CVD prevention. As a remedy, he believed that by legitimizing the syndrome in ATP III "as a medical condition that doctors would recognize and be in tune with" (30), the profession would begin taking obesity seriously. Perhaps it was unclear at the writing of ATP III that ushering in a new medical condition with a very explicit definition, and without much (any) obvious accompanying analysis, begs careful thought to both the intended and unintended consequences.

Other justifications now cited for the utility of the syndrome are as follows. *1*) It "changes medical perspective from a single–risk factor paradigm to one of multiple risk factors" (7,8). But then why hasn't a new condition been defined that will call

attention to other CVD symptoms and risk factors, such as an elevated LDL cholesterol, smoking, shortness of breath, chest pain, older age, etc.? It's hard to imagine that physicians can't very well sort through multiple abnormal test results and that they need help understanding that having many CVD risk factors is not a good thing. 2) Diagnosing the syndrome provides benefit in that the patient now deserves long-term follow-up (7,8). Surely physicians exercise appropriate judgment as to when follow-up is needed without having to construct a syndrome to prompt such action.

Labeling a person with the metabolic syndrome can be very misleading to the physician and the patient. The syndrome is defined by dichotomizing continuous variables and providing no upper limits to any of them. Thus, a person who has an FPG of 105 mg/dl and a systolic blood pressure of 130 mmHg and is only slightly overweight would be classified as having the syndrome. Meanwhile, another person with uncontrolled diabetes, a systolic blood pressure of 165 mmHg, and morbid obesity would also be classified as having metabolic syndrome. Are both individuals at similar risk for a future myocardial infarction or stroke? What if the first person had an LDL cholesterol of 75 mg/dl, was 40 years of age, was female, and had no family history of CVD? Does the presence of the syndrome in that case convey CVD risk above that of an average adult? Does having the syndrome indicate a greater risk of diabetes than just looking at this woman's FPG? How does labeling a person with the syndrome help guide treatment for elevated CVD risk factors?

Alternatively, imagine a 55-year-old man who is very overweight and has hypertension but no other CVD risk factors. Is lifestyle modification not warranted? Does the absence of the syndrome in this case guide treatment? What if the patient also smoked and had an LDL of 160 mg/dl? Is the absence of the syndrome encouraging? What if the man was only obese and had no other risk factor: is lifestyle therapy different or less important because he doesn't have the metabolic syndrome?

The above scenarios highlight a very important concern. If the advent of the metabolic syndrome was meant to call attention to certain risk factors, it could just as easily distract physicians from dealing with other, equally/more important risk factors. It could strike undue fear in the mind of a patient who may think he or she has some ominous disease, or it could lead to complacency in the mind of a high-risk patient who is relieved to know that he didn't have the terrible metabolic syndrome. If the syndrome is meant to stimulate doctors to focus attention on weight control and exercise (lifestyle), what other condition should we create to ratchet up physician attention to smoking cessation, a far more risky lifestyle problem for many teens and adults?

So what should we do?

As stated in the beginning of this commentary, the clustering of certain CVD risk factors is real and important. However, physicians should pay equal attention to all of the well-documented CVD and diabetes risk factors and treat each according to established clinical guidelines. The list is not so long or complex that it is harder to remember than the rest of the vast knowledge required to be a good physician.

Of great importance is the serious condition of being overweight/obese. Its downstream effects result in substantial morbidity and mortality. Overweight/obesity deserves no less attention if it occurs by itself; we shouldn't have to link the problem with other risk factors to justify treatment. Moreover, health professionals should not need any prompting to speak as frankly to a patient about their weight as they do for other potentially embarrassing conditions.

In summary, medicine now operates in an era where substantive scientific evidence is highly valued, if not mandated, before a new medical condition is created and then raised to the level where attention is justified. Without some reasonable understanding of the implications of a disease label (its benefits, risks, costs, who it "captures," and who it misses), the medical profession does a disservice to the public it serves and its credibility is threatened.

The metabolic syndrome as defined is associated with many uncertainties and inconsistencies, and its clinical value is highly questionable if not nonexistent. Indeed, rather than being an instrument that moves medical care in a valuable direction, it has all the qualities that could easily misdirect care, mislead patients, create uncertainty, and lead to unnecessary health care costs. For example, the cost-effectiveness and justification for stand-alone fitness and psychological counseling programs under the guise of treating a unique disease seem unclear at best (31).

No one questions the belief that there are many cardiometabolic risk factors that deserve attention. Being overweight or obese is one such important factor. Fortunately, we have guidelines and well-documented therapies that reduce all of these CVD and diabetes risk factors, individually or in combination, and lifestyle modification is the cornerstone of treatment. To make this paradigm any more complex seems pointless.

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