guideline panels have come to believe that this concept should be further simplified into a recognizable entity that will facilitate the clinical management of patients. Because of the variable clinical face of the syndrome, there will be continuing debate about the best way to bring the concept into clinical practice. The stimulus provided to the medical community by introduction of the ATP III definition of metabolic syndrome and related definitions nonetheless appears to have justified transforming a theory into a usable clinical tool. It is one of several tools that may help to reduce comorbidities that otherwise will be inevitable because of the expanding prevalence of obesity in the United States and worldwide (20).

References

Counterpoint Just Being Alive Is Not Good Enough

GERALD REAven

Although Dr. Scott Grundy assures us that the Adult Treatment Panel III (ATP III) version of the metabolic syndrome is still alive (1), the real question is whether its continued existence provides us with any useful information. Just being alive is not enough, for as Sportin’ Life points out in Gershwin’s Porgy and Bess, “Methuselah lived 900 years, but who calls it living, when no gal will give in, to him that’s 900 years.”

Does Diagnosing the Metabolic Syndrome Have Clinical Utility?

Before addressing the substance of Dr. Grundy’s comments, I must defend myself against his charge that I have limited my critical comments to the ATP III version of the
metabolic syndrome. I am not xenophobic, and in a recent editorial addressed what I perceived to be the drawbacks of both the ATP and WHO versions of the metabolic syndrome (2). The most obvious problem for me is the notion that making a positive diagnosis of the metabolic syndrome, compared with a negative one, helps guide clinical decisions. For example, WHO criteria would not lead to a diagnosis of the metabolic syndrome in an apparently healthy, normotensive man, body mass index of 27.8 kg/m², with fasting plasma glucose and triglyceride (TG) concentrations of 111 mg/dL (6.16 mmol/L) and 185 mg/dL (2.09 mmol/L), respectively, if he had a HDL-cholesterol (HDL-C) concentration of 37 mg/dL (0.96 mmol/L). By implication, this person would not be at increased risk of cardiovascular disease (CVD). On the other hand, given essentially identical findings, another man, with a HDL-C concentration of 33 mg/dL (0.85 mmol/L), has the metabolic syndrome by WHO criteria and is, by definition, at increased CVD risk. Is the CVD risk any different in these 2 men? Would not the clinical approach be similar in both? More of this later, but suffice it to say that this example puts into real life context a major reason why I believe that efforts to establish diagnostic criteria for the metabolic syndrome, whether ATP III or WHO, offer little in the way of clinical utility.

If I understand Dr. Grundy’s comments, the impetus for the ATP to propose criteria to diagnose the metabolic syndrome stemmed from the increasing prevalence of obesity in the United States, and a view that “[T]he concept of the metabolic syndrome appeared to be the best way to identify those persons in greatest need of clinical intervention” (1). According to Dr. Grundy, “the metabolic syndrome consists of a constellation of ‘metabolic risk factors’ for ASCVD [atherosclerotic cardiovascular disease] that associate with obesity, namely, atherogenic dyslipidemia, increased blood pressure, increased glucose, a prothrombotic state, and a proinflammatory state” (1). However, this constellation is closely associated with insulin resistance, is present in nonobese individuals, and occurs primarily in those obese individuals who are also insulin resistant (3–18). It seems highly likely that the increased prevalence and/or severity of these abnormalities in obese individuals explain why they are at increased CVD risk, not simply because they are obese. In support of this view are the results of a recent analysis by Ninomiya et al. (19) of data from the Third National Health and Nutrition Examination Survey. In most instances, these authors could document significant relationships between the individual components of the metabolic syndrome with CVD, stroke, and CVD/stroke, with the notable exception of abdominal obesity as determined by measurement of waist circumference (WC). As a result, they suggested that the “absence of an independent association of high WC with prevalent diseases in these data may reflect an indirect effect of high WC through other components of the syndrome” (19).

The comments of Ninomiya et al. (19) echo my own view that the focus should be directed to the CVD risk factor status of the components of this constellation rather than on whether or not individuals are obese or if they meet 3, rather than only 2, of the ATP III criteria for making a diagnosis of the metabolic syndrome. To return to the same refrain, does anyone think, assuming “normal” values for glucose and HDL-C, that an individual with increased blood pressure and TG concentrations, but not abdominally obese by ATP III criteria, is at less CVD risk than a person with similar values who also happens to have an “abnormal” WC?

Although I agree that being obese increases risk of CVD, I find it somewhat strange that the ATP III has assigned it such a central role (no pun intended) in diagnosing the metabolic syndrome. For example, a person with a fasting TG of 215 mg/dL (2.43 mmol/L) or a fasting glucose of 120 mg/dL (6.66 mmol/L) is clearly at increased CVD risk because of these abnormalities. A normal WC by ATP III criteria does not mean that the above changes in TG and glucose concentrations will not be present, anymore than being abdominally obese means that they will be present. I find this emphasis on measuring WC even more confusing in that I cannot find any directions in the report of the ATP III describing how to do it. The absence of this information does not seem trivial in light of the recent report (20) pointing out that studies demonstrating the relationship between increased abdominal obesity and adverse clinical consequences have relied on at least 14 different methods to quantify WC and that even the 4 most commonly used approaches yielded quite different absolute values for WC. To further confound this issue, a recent report from the WHO, expressing concern that the untoward effects of obesity will vary as a function of ethnicity, proposed that it will be necessary to develop ethnic-specific values to identify overweight/obese individuals at greatest risk (21). Why go to all this trouble? Why not simply measure blood pressure and fasting plasma glucose, TG, and HDL-C concentrations and initiate whatever interventions are appropriate to deal with any abnormalities discerned. One does not need a diagnosis of the metabolic syndrome to act in a clinically useful fashion.

I also question the manner in which the ATP III uses the plasma glucose concentration. Although they set a lower limit [forgetting that it seems to be a moving target, yesterday 110 mg/dL (6.10 mmol/L), today 100 mg/dL (5.55 mmol/L), and tomorrow, who knows?], they apparently did not see a need for an upper limit. It is not obvious to me why a patient with type 2 diabetes needs an additional diagnosis; however, that is what has resulted from the use of the ATP III criteria, and most, if not all, of the enormous number of reports describing the prevalence of the metabolic syndrome have included patients with diabetes. The importance of making a diagnosis of type 2 diabetes to initiate appropriate therapy is self-evident. However, once established, the additional clinical benefit from knowing whether the patient has the

[1] Ninomiya et al. (19)
[2] Grundy (1)
metabolic syndrome is not obvious. Current treatment guidelines from the American Diabetes Association (22) emphasize the importance of treating all of the abnormalities more likely to occur in patients with type 2 diabetes, e.g., dyslipidemia, hypertension, and renal impairment, and discuss therapeutic approaches to be considered. I truly do not think we need the metabolic syndrome to decide how to treat patients with type 2 diabetes.

In conclusion, I believe that measuring blood pressure and plasma glucose, TG, and HDL-C concentrations provides important clinical information, and these data can form the basis for rational therapeutic decisions involving not just lifestyle, but potential pharmacologic interventions as well. I do not believe that focusing on whether the patient has, or does not have, the metabolic syndrome is useful, and I worry that a patient who might have only a high TG and a low HDL-C will not receive appropriate treatment if they do not qualify for a diagnosis of the metabolic syndrome.

Has the Introduction of Criteria for Diagnosing the Metabolic Syndrome Stimulated Basic, Clinical, or Epidemiologic Research?

As pointed out by Criqui (23) in a recent commentary, “a PubMed search in March 2005, with the key word ‘metabolic syndrome’, yielded >10,000 references.” If the number of citations were the only measure, the introduction of the metabolic syndrome has certainly been a success. However, it is important to separate the theoretical construct of a “metabolic syndrome” from the effort by the ATP III to create a new diagnostic category. Studies focused on understanding the pathophysiology of insulin resistance have greatly expanded the number of abnormalities associated with defects in insulin action (24, 25). At the same time, a great deal has been learned concerning the relationship between these abnormalities and the development of clinical syndromes such as CVD, type 2 diabetes, essential hypertension, nonalcoholic fatty liver disease, certain forms of cancer, polycystic ovary syndrome, and sleep-disordered breathing (24, 25). This research activity was not stimulated by the introduction of diagnostic criteria for a metabolic syndrome by either the WHO or the ATP III.

Dr. Grundy poses as an example of the stimulation of research what he seems to view as two polarized positions: the cause of the metabolic syndrome is insulin resistance vs the cause of the metabolic syndrome is inflammation. I do not see this in quite the same manner, as there is evidence that insulin resistance and inflammation are associated, and the nature of that relationship is certainly worthy of study. However, I do not believe that investigation aimed at understanding the relationship between insulin resistance and inflammation will be focused on, as suggested by Dr. Grundy, “biological mechanisms underlying the metabolic syndrome” as defined by the ATP III. Is it possible to evaluate the biological mechanisms underlying the metabolic syndrome when phenotypes might vary widely from person to person? For example, imagine 2 individuals with the ATP III version of the metabolic syndrome: one is abdominally obese, with a fasting glucose of 103 mg/dL (5.72 mmol/L) and a blood pressure of 140/85 mmHg, and the other has the same blood pressure, with a TG of 180 mg/dL (2.03 mmol/L) and an HDL-C of 30 mg/dL (0.78 mmol/L). How likely are these 2 individuals to have the same biological mechanisms underlying the metabolic syndrome? My guess is not very likely. A more fruitful approach would be to address such issues as the relationship between insulin resistance and inflammation: for example, whether the relationship is causal or whether both changes are secondary to some more basic abnormality; and how insulin resistance and inflammation interact in increasing risk of CVD, type 2 diabetes, and the transformation of nonalcoholic fatty liver disease to non-alcoholic steatohepatitis. How can there be a common etiology for a diagnostic category based on satisfying 3 of 5 arbitrarily defined criteria when any combination of the 3 will define the same phenotype as any other trio of abnormalities?

I will acknowledge that the introduction of criteria for diagnosing the metabolic syndrome has certainly stimulated epidemiologic research. On the other hand, I am not sure that we have learned a great deal from the effort. For example, I am not convinced, and this feeling may be unique to me, that knowing the prevalence of the ATP III version of the metabolic syndrome in every country in the world and within each of these countries as a function of differences in age, ethnic group, urban vs rural dwelling, and socioeconomic status provides much useful information. I think the utility of these observations is diminished by the fact that the 5 criteria chosen, as well as the cutpoints, are arbitrary and represent no more than the best guesses of a committee. Furthermore, the diagnosis may or may not include patients with manifest diabetes, different criteria are used to define an abnormal glucose value, and there is often little discussion as to which of the components is most responsible for a positive diagnosis. Dr. Grundy states, “the presence of the metabolic syndrome as a whole carries a substantially higher relative risk for both ASCVD and diabetes than in its absence”, an observation that seems to me to be neither surprising nor offering a compelling defense of its clinical utility. As Criqui (23) eloquently points out, “more than a half-century of prospective epidemiologic research has identified several modifiable independent CVD risk factors, including cigarette smoking, hypertension, insulin resistance/diabetes, and dyslipidemia.” He then goes on to point out that “our concern with the obesity epidemic rightly focuses our attention on the risk factors linked to obesity, which cluster in the MS-NCEP [National Cholesterol Education Program–Adult Treatment Panel III definition of metabolic syndrome], but nothing we have learned in studying the MS-NCEP changes what we learned in earlier epidemiological studies.”
Does the ATP III Definition of the Metabolic Syndrome Have Any Redeeming Virtues?

Approximately one-third of an apparently healthy population is sufficiently insulin resistant to be at increased risk to develop a variety of adverse clinical outcomes that now include type 2 diabetes, CVD, essential hypertension, polycystic ovary syndrome, nonalcoholic fatty liver disease, several forms of cancer, and sleep-disordered breathing (24). The ATP III focused on the increased CVD risk that exists in insulin-resistant individuals, proposed creating the diagnostic category of the metabolic syndrome, and provided criteria with which to identify individuals who merit this diagnosis. I clearly am not impressed with this notion and question the utility of either form of the metabolic syndrome, ATP III or WHO. I am also quite concerned as to the risks that might result from failure to initiate appropriate efforts to reduce CVD risk in individuals not meeting the diagnostic criteria. Perhaps the greatest benefit elicited by publication of the ATP III definition of the metabolic syndrome is to emphasize the importance of the cluster of CVD risk factors associated with insulin resistance. The greatest potential drawback then becomes a focus on whether a patient meets the ATP III diagnostic criteria for the metabolic syndrome rather than addressing the abnormalities associated with insulin resistance and compensatory hyperinsulinemia.

References