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Review

The Metabolic Syndrome: Requiescat in Pace

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Values for insulin-mediated glucose disposal vary continuously throughout a population of apparently healthy individuals, with at least a sixfold variation between the most insulin sensitive and most insulin resistant of these individuals. The more insulin resistant a person, the more insulin must be secreted to prevent decompensation of glucose tolerance. Insulin resistance is not a disease, but a description of a physiologic state, and approximately one third of an apparently healthy population is sufficiently insulin resistant to be at increased risk to develop a cluster of abnormalities and related clinical syndromes. The primary value of the concept of insulin resistance is that it provides a conceptual framework with which to place a substantial number of apparently unrelated biological events into a pathophysiological construct. In contrast, the metabolic syndrome was introduced as a diagnostic category to identify individuals that satisfy three of five relatively arbitrarily chosen criteria to initiate lifestyle changes with the goal of decreasing risk of cardiovascular disease. Consequently, the value of the notion of the metabolic syndrome must be considered not in pathophysiologic terms, but as a pragmatic approach to obtain a better clinical outcome. In this review an effort is made to critically evaluate the concept of the metabolic syndrome, the criteria chosen to identify individuals with the syndrome, and the clinical utility of making, or not making, a diagnosis of the metabolic syndrome.
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In 2001, the Adult Treatment Panel III (ATP III)[1] of the National Cholesterol Education Program proposed criteria for diagnosing what they designated the metabolic syndrome *(1)*. Since the original report by Ford et al. *(2)* in 2002 describing the prevalence of the metabolic syndrome in the United States, multiple papers have been published addressing the same issue. As an example of this phenomenon, I cite 14 articles *(3–16)* that represent a small sample of those published on this topic in 2004; they were based primarily on retrospective analyses of population-based studies, conducted in several countries, with experimental data gathered for a variety of different reasons, in groups differing in terms of age, sex, and ethnicity. Although this burst of creative activity has led to an enormous amount of published data, it is not clear that it has led to the delivery of any new information of significant utility to the practicing clinician. In fact, as will be discussed subsequently, if taken at face value, there is a real possibility that use of the ATP III criteria could do more harm than good. At the least, it might be useful to take a somewhat skeptical look at the clinical implications of implementing the diagnostic criteria proposed by the ATP III, and the effort to address this issue is the justification for this presentation.

Definition of the Metabolic Syndrome

The establishment of criteria for diagnosing what the ATP III report termed the metabolic syndrome *(1)* represented an effort to acknowledge the importance of resistance to insulin action, and its consequences, as increasing the risk of cardiovascular disease (CVD). The ATP III recognized *(1)* the importance as CVD risk factors of what they called a "constellation of lipid and non-lipid risk factors of metabolic origin," designated this cluster as the metabolic syndrome, and stated that "this syndrome is closely related to insulin resistance." Table 1 lists the five criteria selected by the ATP to identify individuals with the metabolic syndrome [abdominal obesity, impaired fasting glucose, high triglyceride (TG) and low HDL-cholesterol (HDL-C) concentrations, and increased blood pressure], and reflects their view that insulin resistance is at the root of the problem. The primary goals of the ATP III in establishing criteria for making the diagnosis of the metabolic syndrome were to identify individuals at increased

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[1] Nonstandard abbreviations: ATP III, Adult Treatment Panel III; CVD, cardiovascular disease; TG, triglyceride; HDL-C, HDL-cholesterol; WC, waist circumference; BMI, body mass index; ADA, American Diabetes Association; IFG, impaired fasting glucose; and IGT impaired glucose tolerance.

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Table 1. ATP III criteria for diagnosing the metabolic syndrome.[a]

- Abdominal obesity
  Men: WC >40 inches
  Women: WC >35 inches
- Fasting glucose ≥1100 to <1260 mg/L
- Blood pressure ≥130/80 mm Hg
- TGs ≥1500 mg/L
- HDL-C
  Men: <400 mg/L
  Women: <500 mg/L

[a] The metabolic syndrome is present when three or more of the five criteria are met.

CVD risk and to use this information to initiate lifestyle changes to decrease this risk.

The individual criteria listed in Table 1 appear to have been selected because they tend to cluster together as well as to occur more commonly in insulin resistant individuals *(17, 18)*. In addition, they all have been associated with increased CVD risk *(19–23)*. However, before focusing on the individual components that make up the diagnostic criteria for the metabolic syndrome, some general comments about the deliberations that led to their creation are worthy of note. Perhaps the most crucial issue is that the diagnostic criteria for the metabolic syndrome did not result from a prospective study and do not represent the outcome of an evidence-based process, but are a reflection of the best estimates of a panel of "experts". Furthermore, not only are the cut points for the five chosen criteria arbitrary, there is no reason to believe that the individual elements of the metabolic syndrome are equally reflective of either the presumed basic defect or the risk of CVD. Indeed, it is not clear what led to the decision to select five criteria (why not four or six?), nor why satisfying any three of five arbitrary criteria has more clinical utility than any two others. In light of the above considerations, there is ample reason to question the clinical utility of making a positive (or negative) diagnosis of the metabolic syndrome.

Furthermore, before critically examining the criteria proposed for making the diagnosis of the metabolic syndrome, it is essential to emphasize that the report of the ATP III focused entirely on the role of insulin resistance as increasing risk of CVD. It is now clear, however, that a variety of abnormalities and clinical syndromes are more likely to occur in insulin-resistant individuals. Specifically, in addition to CVD, insulin-resistant individuals are at increased risk to develop type 2 diabetes, essential hypertension, nonalcoholic liver disease, polycystic ovary disease, certain forms of cancer, and sleep apnea (Table 2). These issues cannot be discussed in detail in the context of this presentation, but such information is available in two recent review articles *(24, 25)*.

Table 2. Clinical syndromes associated with insulin resistance.

- Type 2 diabetes
- CVD
- Essential hypertension
- Polycystic ovary syndrome
- Nonalcoholic fatty liver disease
- Certain forms of cancer
- Sleep apnea

Examining the Individual Components of the Metabolic Syndrome

WAIST CIRCUMFERENCE

The inclusion of a measure of excess adiposity [waist circumference (WC)] as one of ATP III criteria for diagnosing the metabolic syndrome seems incongruent as, in contrast to other criteria, it is not a consequence of insulin resistance. Instead, obesity is a lifestyle variable that, along with physical inactivity, has an adverse effect on insulin-mediated glucose disposal *(26–28)*, thereby increasing chances that the abnormalities and clinical syndromes associated with insulin resistance will develop. Stated more specifically, insulin resistance/hyperinsulinemia does not cause obesity; obesity is a physiologic variable that increases the likelihood that an individual will be insulin resistant. To understand the metabolic syndrome in pathophysiologic terms, it is necessary that obesity be viewed as contributing to insulin resistance/hyperinsulinemia, in contrast to the other four criteria, which represent changes that are more likely to occur in insulin resistant/hyperinsulinemic individuals.

The fact that obesity is not a consequence of insulin resistance/hyperinsulinemia should not obscure the fact that the more overweight/obese an individual, the more likely it is that the individual will be sufficiently insulin resistant to be at increased risk to develop one or more of the adverse clinical consequences associated with the defect in insulin action. This is clearly of great clinical significance in light of the current worldwide epidemic of obesity. On the other hand, although being overweight/obese increases the chances of an individual being significantly insulin resistant, by no means are all overweight/obese individuals insulin resistant, and, of greater clinical relevance, weight loss in overweight/individuals who are not insulin resistant does not lead to substantial clinical benefit *(26–30)*. Therefore, being overweight/obese is a finding that should alert the healthcare provider to the possibility that an individual is insulin resistant and at increased risk to develop the clinical syndromes listed in Table 2. As such, the question then becomes one of the most effective way to identify these individuals.

The ATP III has emphasized the importance of WC as the estimate of adiposity on the premise that it is an index more closely related to insulin resistance and its consequences than generalized obesity as determined by body mass index (BMI). However, its superiority as a clinical

tool can be questioned. At the simplest level, the values of the two variables were highly correlated in a recent analysis *(31)* of data from ~20 000 participants in the National Health and Nutrition Survey (NHANES) from 1988–1994 and 1999–2000. More specifically, the *r* values were >0.9 in every subgroup analyzed and were essentially identical irrespective of differences in sex, age, or ethnicity.

Height and weight are routinely measured in most healthcare facilities in a reasonably simple fashion, and the BMI is easily calculated by referring to simple tables. In contrast, the following paragraph contains the directions for measuring WC according to the NHANES protocol.

> The subject stands and the examiner, positioned at the right of the subject, palpates the hip bone to locate the iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn, and then crossed with a vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor and the tape is snug, but does not compress the skin. The measurement is made at normal minimal inspiration.

To the best of my knowledge, data as to the reproducibility of measurements of WC at any given clinical site, let alone from site to site, when following this precise protocol, are not available. It also seems reasonable to express skepticism concerning the likelihood that measurements of WC will be performed with this same degree of seriousness, and in a uniform manner, in health centers throughout the United States.

Furthermore, as pointed out in a recent report *(32)*, it appears 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 even the 4 most commonly used approaches yielded quite different absolute values for WC. This issue is further confounded by a recent report from the WHO expressing concern that because the untoward effects of obesity will vary as a function of ethnicity, it will be necessary to develop ethnicity-specific values to identify overweight/obese individuals at greatest risk *(33)*

Given the information discussed above, it seems counterproductive to think that it will be possible to develop specific cut points for WC, varying by ethnicity, that will be measured accurately to satisfy one of the diagnostic criteria of the ATP III version of the metabolic syndrome. When these pragmatic issues are coupled with the fact that being overweight/obese simply increases the likelihood that an individual will be insulin resistant, it seems most sensible to simply measure height and weight, assess BMI, and know that having a BMI >25.0 kg/m^2 increases the chances that an individual will be insulin resistant in the same way as, for example, having a family history of type 2 diabetes, essential hypertension, or CVD; being of non-European ancestry; or having acanthosis nigricans. It should alert one to look for the manifestations of insulin resistance–no more, no less.

In summary, being overweight/obese increases the likelihood that an individual will be sufficiently insulin resistant to develop one of the adverse clinical outcomes listed in Table 2. Thus, obesity is similar to several other findings from the medical history and physical examination that make it more likely that an individual will be insulin resistant. If a method of quantifying the degree of obesity is desired, it appears that BMI and WC are tightly correlated, and measurement of BMI is a simpler and more effective way to accomplish that task.

FASTING PLASMA GLUCOSE CONCENTRATION

The American Diabetes Association (ADA) has introduced the category of impaired fasting glucose (IFG) to classify individuals as having "prediabetes", and initially *(34)* suggested that individuals with a fasting plasma glucose concentration between 1100 and 1250 mg/L merited that designation. Because a fasting glucose ≥1260 mg/L is diagnostic of diabetes, a disease unequivocally known to increase CVD risk, it seems likely that the selection of IFG by the ATP III to aid in the diagnosis of the metabolic syndrome stemmed from the creation of this new diagnostic criterion by the ADA. Although there is substantial epidemiologic evidence that the higher the plasma glucose concentration, the more likely an individual is to develop type 2 diabetes, it is not as clear that the use of IFG provides a particularly effective way to identify either the presence of insulin resistance or to predict CVD risk. Values of insulin-mediated glucose disposal are distributed continuously throughout the nondiabetic population *(35)*, and the results of two prospective studies suggest that the third of the population that is most insulin resistant is at significantly increased risk to develop one or more of the clinical syndromes listed in Table 2 *(36, 37)*. When this definition of clinically significant insulin resistance was applied to a population of 490 apparently healthy individuals, only 27 (5.5%) had IFG, and 17 of these 27 (63%) were in the insulin-resistant tertile *(38)*, giving a test with great specificity (327 of 337, or ~ 97%), but low sensitivity (17 of 163, or ~10%). The sensitivity of identifying insulin-resistant individuals can be increased essentially threefold by measuring plasma glucose concentration after an oral glucose load and using the ADA diagnostic criterion for impaired glucose tolerance (IGT = plasma glucose concentration of 1400–1990 mg/L 120 min after a 75-g oral challenge) *(38)*. Furthermore, ~25% of those in the most insulin-resistant tertile did not have prediabetes as defined by either IFG or IGT *(38)*.

It is apparent from these findings that the presence of IFG as initially proposed by the ADA, and adopted by the ATP III, occurs too infrequently to be very useful in the diagnosis of either insulin resistance or the metabolic syndrome. Indeed, if the goal is to identify individuals at

increased risk of CVD, the results of the DECODE study strongly suggest that it would be more useful to look for IGT rather than IFG *(39)*. More recently, the ADA has modified its definition of IFG and now suggests that this diagnosis be applied to individuals whose fasting plasma glucose concentration is 1000–1250 mg/L *(40)*, and the ATP III has followed suit by modifying their fasting plasma glucose criterion accordingly *(41)*. One reason for the ADA to lower the fasting plasma glucose concentration for the diagnosis of IFG was to capture more individuals with IGT, and Tai et al. *(42)* have confirmed that this was the case in the Singapore CVD Cohort Study. These authors pointed out that although the prevalence of IFG increased (from 9.5% to 32.3%) with the revised criteria, associated with an increase in the number identified at risk to develop type 2 diabetes and CVD, identifying IGT was a more effective way to accomplish that goal. In contrast, Borch-Johnsen et al. *(43)*, using data from multiple countries, warned that only a relative minority of those identified with the proposed ADA modification of IFG would have IGT and that the CVD risk profile would be significantly lower than in those individuals meeting the original diagnostic criterion. Finally, the authors of both publications *(42, 43)* expressed great concern that adoption of the newly proposed ADA definition of IFG would have adverse public health consequences, with Borch-Johnsen et al. *(43)* warning that use of the proposed new definition of IFG would create "a pandemic of prediabetes." Obviously, the same concerns apply to incorporating the revised ADA criterion for IFG in the guidelines for diagnosing the metabolic syndrome.

In the most general sense, the higher the fasting plasma glucose concentration, the more likely an individual is to be insulin resistant and at increased risk for developing the clinical syndromes listed in Table 2. Determining the fasting plasma glucose concentration is clearly of importance for identifying patients with type 2 diabetes and subsequently leading to the initiation of appropriate glycemic control. On the other hand, knowledge of the fasting plasma glucose concentration does not provide a particularly useful surrogate estimate of insulin resistance, accounting for only ~5–15% of the variance (depending on degree of adiposity) in insulin-mediated glucose disposal in the population at large *(44)*. If the plasma glucose concentration is to be used for identifying insulin-resistant individuals with increased risk to develop CVD, it seems that measurements made after an oral glucose challenge offer the most clinical utility *(38, 39, 42, 43)*. In the absence of obtaining this information, neither cut point for identifying patients with the metabolic syndrome proposed by the ATP III seems to be particularly useful.

DYSLIPIDEMIC COMPONENTS

The dyslipidemic components of the metabolic syndrome, a high TG and a low HDL-C concentration, are the ATP III criteria linked most closely to both insulin resistance and CVD risk. For example, differences in plasma TG concentration can account for ~36% of the variation in insulin-mediated glucose disposal in the same population in which fasting plasma glucose concentration accounted for only 5–15% of the variability. Indeed, the relationship between plasma TG concentration and insulin-mediated glucose disposal is comparable to that between fasting plasma insulin concentration and insulin action, a commonly used surrogate estimate of insulin resistance *(35)*.

The ability of a low HDL-C to predict CVD risk has been known for many years *(45)*, and although issues have been raised concerning the role of an increase in TG concentration as an "independent" CVD risk factor *(46)*, there is certainly evidence in support of that notion *(21, 47)*. Furthermore, although not cited as one of the criteria for diagnosing the metabolic syndrome, the atherogenic lipoprotein profile associated with insulin resistance also includes a decrease in LDL particle diameter (small, dense LDL) and the postprandial accumulation of TG-rich remnant lipoproteins *(48, 49)*, and these changes have also been shown to be associated with increased CVD risk *(50, 51)*. Furthermore, evidence from both the Helsinki Heart Study and the VA-HIT study demonstrated that the use of gemfibrozil, an agent that decreases plasma TG and increases HDL-C concentrations, significantly decreased CVD risk *(52, 53)*. Of particular interest in this context is the recent analysis of the VA-HIT data indicating that individuals who had the highest plasma insulin concentrations at baseline, and were presumably the most insulin resistant, benefited the most from gemfibrozil treatment *(54)*.

Although it is possible to question the absolute cut points proposed by the ATP III for evaluating the clinical significance of plasma TG and HDL-C measurements, there is obviously abundant information suggesting that the dyslipidemic criteria proposed by the ATP III are characteristic of insulin-resistant/hyperinsulinemic individuals, are highly predictive of CVD risk, and when the conditions are treated, lead to a decreased incidence of CVD. As such, they are quite different from either the WC or the fasting plasma glucose concentration criteria. More importantly, they raise a fundamental question as to the clinical utility of the metabolic syndrome that every healthcare provider must face: should appropriate treatment be initiated in a patient with a high plasma TG and a low HDL-C concentration, even if they do not have prediabetes or abdominal obesity? The answer to this question begins to focus the discussion on the implications of making, or not making, a diagnosis of the metabolic syndrome as defined by the ATP III.

BLOOD PRESSURE

The most complicated relationship between insulin resistance/hyperinsulinemia, the ATP III version of the metabolic syndrome, and CVD relates to the role of essential hypertension. The problem stems from the fact that no more than 50% of patients with essential hypertension are

insulin resistant *(55)*, but that it is this subset of patients who are at greatest CVD risk *(56–58)*. For example, patients with essential hypertension with electrocardiograph evidence of ischemic changes are somewhat glucose intolerant and hyperinsulinemic compared with either a normotensive control group or patients with essential hypertension whose electrocardiograms are entirely normal *(56)*. Not surprisingly, measurement of insulin-mediated glucose disposal demonstrated that patients with essential hypertension and ischemic electrocardiograph changes were insulin resistant and that the dyslipidemic changes associated with insulin resistance/hyperinsulinemia were present in these individuals compared with normotensive individuals or hypertensive patients with normal electrocardiograms.

The link between the dyslipidemia present in insulin-resistant/hyperinsulinemic patients with essential hypertension and CVD is consistent with results of two reports from the Copenhagen Male Study. In the first publication, Jeppesen et al. *(57)* showed that the development of CVD in individuals with a high TG and a low HDL-C concentration was independent of differences in baseline systolic or diastolic blood pressure. In contrast, the higher either systolic ($P < 0.001$) or diastolic ($P < 0.03$) blood pressure was at the beginning of the study, the greater the incidence of CVD in those without the dyslipidemic changes associated with insulin resistance.

In a second study *(58)*, 2906 participants in the Copenhagen Male Study were divided into three groups on the basis of their fasting plasma TG and HDL-C concentrations. Patients with hypertension whose plasma TG concentration was in the upper third of the population, associated with a plasma HDL-C concentration in the lower third, were at greatest CVD risk, whereas CVD risk was not increased in those patients who did not have the dyslipidemia characteristic of insulin resistance/hyperinsulinemia.

The evidence summarized above provides substantial support for the view that the CVD risk associated with increases in blood pressure is significantly increased when the hemodynamic abnormality is present in insulin-resistant individuals. Consequently, it may be more important from a clinical standpoint to focus on whether an increase in blood pressure is associated with the dyslipidemic manifestations of insulin resistance, rather than questioning if the patient in question meets the diagnostic criteria for the metabolic syndrome.

Summary

Values for insulin-mediated glucose disposal vary continuously throughout a population of apparently healthy individuals, with at least a sixfold variation between the most insulin sensitive and most insulin resistant of these individuals *(35)*. Thus, there is no objective way to classify an individual as being insulin resistant. We have attempted in two prospective studies to develop an operational definition of insulin resistance, and the results of these efforts have led us to suggest that approximately one third of an apparently healthy population is sufficiently insulin resistant to develop significant clinical disease *(36, 37)*. It is essential to emphasize at this point that insulin resistance is not a disease, but a description of a physiologic state that greatly increases the chances of an individual developing several closely related abnormalities and associated clinical syndromes. Insulin resistance does not necessarily lead to the clinical syndromes listed in Table 2, and to various degrees, the syndromes can all occur in the absence of insulin resistance. The primary value of the concept of insulin resistance is that it provides a conceptual framework with which to place a substantial number of apparently unrelated biological events into a pathophysiologic construct. Its primary goal is not to make a diagnosis but to increase understanding of why, for example, a woman with polycystic ovary syndrome is more likely to develop type 2 diabetes than a woman with a normal menstrual history *(59)*. This does not imply that the notion of insulin resistance is without clinical utility. For example, it explains why women with polycystic ovary syndrome should be monitored closely for evidence of deterioration of glucose tolerance *(60)*, and the apparent link between insulin resistance/compensatory hyperinsulinemia and the clinical course of breast cancer *(61)* provides an obvious mechanistic target with which to experiment with new treatment options.

In contrast, the metabolic syndrome is focused on only one of the clinical syndromes associated with insulin resistance listed in Table 2, and the rationale for its implementation is to make a diagnosis to initiate lifestyle changes with the goal of decreasing CVD risk. Consequently, its value must be considered not in pathophysiologic terms, but as a pragmatic approach to obtain a better clinical outcome. Thus, the fact that obesity is a variable that contributes to insulin resistance, not a consequence of the defect in insulin action, does not necessarily detract from the usefulness of the metabolic syndrome. However, the possibilities that the measure of obesity listed in Table 1 may be less than ideal and that the values for WC may be most applicable to individuals of European ancestry, are issues that need further discussion. Similarly, what is the value of IFG as a diagnostic criterion when only ~5% of an apparently healthy population has that abnormality?

Despite the potential limitations of the criteria that have been proposed to diagnose the metabolic syndrome, the most fundamental question relates to the clinical utility of using them to decide whether an individual does, or does not, deserve that sobriquet. In that context, imagine two men, both of whom have blood pressures and plasma TG concentrations high enough to satisfy the ATP III criteria to merit the diagnosis of the metabolic syndrome, but neither had a large enough waist or a high enough fasting plasma glucose to qualify for that diagnosis. In fact, the only apparent difference between them was that the HDL-C concentration was 380 mg/L in one

of them, whereas the other one had a value of 420 mg/L. By definition, one man has the metabolic syndrome; the other does not. Are these individuals fundamentally different? Would the treatment options differ in any substantive way? Does knowing that a patient has an increased blood pressure, as well as a high plasma TG concentration, not merit appropriate clinical intervention? Does it matter that the patient does not have the metabolic syndrome, because his WC, fasting plasma glucose concentration, and HDL-C concentration do not meet the arbitrary criteria established by the ATP III?

Perhaps the point is made even more emphatically if attention is turned to patients whose fasting plasma glucose concentrations merit the diagnosis of type 2 diabetes. These individuals clearly have a disease, and every year the ADA publishes treatment guidelines for these patients to decrease their risk of developing both the microangiopathic and macrovascular complications of type 2 diabetes. Is there any clinical utility in determining whether these patients have the metabolic syndrome? This rhetorical question was addressed in the The Casale Monferrato Study, which evaluated the ability of the WHO definition of the metabolic syndrome to predict all-cause and cardiovascular mortality in 1565 patients with type 2 diabetes *(62)*. The results of this study indicated that "categorizing type 2 diabetic subjects as having or not having the metabolic syndrome does not provide further prediction compared with the knowledge of its single components." Parenthetically, in the same edition of *Diabetes Care*, the ATP III criteria for diagnosing the metabolic syndrome were applied to the populations of the San Antonio Heart Study and the Mexico City Diabetes Study *(63)*, with the finding that "the metabolic syndrome is inferior to established predicting models for type 2 diabetes or CVD." This latter finding is consistent with an earlier publication *(30)* showing that simple measurement of plasma TG and HDL-C concentrations provided information that was essentially as useful as the ATP III version of the metabolic syndrome in identifying those apparently healthy individuals who were sufficiently insulin resistant to be at increased risk to develop the clinical syndromes listed in Table 2.

In conclusion, it appears that making the diagnosis of the metabolic syndrome does not bring with it much in the way of pathophysiologic understanding or clinical utility, and deciding that individuals do not have it because they fail to satisfy three of five arbitrarily chosen criteria may withhold relevant therapeutic intervention. Does the APP III concept of the metabolic syndrome have any redeeming virtues? That is a question that only the reader can answer.

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