Perspective

The Individual Components of the Metabolic Syndrome: Is There a Raison d'Etre?

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Introduction

The last few years have witnessed a veritable torrent of publications concerning a new diagnostic category: the metabolic syndrome (MetS). At least three different sets of criteria have been published with which to make this diagnosis [1–3], and although they contain the same basic components, they differ dramatically in basic philosophy and how they are used to make a diagnosis. Furthermore, despite the large number of publications devoted to the metabolic syndrome, questions have been raised concerning both its clinical and pedagogical utility [4–7]. Perhaps the most direct assault on the notion has been issued in a joint report [5] from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), in which it is stated that "providers should avoid labeling patients with the term 'metabolic syndrome'. In contrast, a joint position paper from the American Heart Association and the National Heart, Lung, and Blood Institute, stoutly defends the concept [8].

In light of this on-going debate as to the clinical utility of making a diagnosis of the MetS, surprisingly little attention has been paid to the ubiquity of the individual components that make up the diagnostic criteria of all the definitions of the MetS. How is possible that the same components appear in all three definitions? Are they simply unrelated cardiovascular disease (CVD) risk factors? If so, why not include hypercholesterolemia? Alternatively, is it because the only explanation for the components clustering in this fashion is that they are all related to a common unifying pathophysiology? The report from the ADA/EASD doesn't entirely think so, and concludes that "Although the studies reviewed above question the hypothesis that insulin resistance/hyperinsulinemia is the major underlying pathological process, it must be remembered that the clustering of CVD risk factors has been well documented, and thus it is likely (but not assured) that there is some underlying etiology."

In this presentation I will respond to their statement, and summarize the evidence indicating that the abnormalities that comprise all versions of the MetS do not 'cluster' together by accident, and that a defect in insulin action, and its consequences, plays a fundamental role in the development of the CVD risk factors that comprise all versions of the MetS. Indeed, given available information, it is the only way to explain the clustering of the specific components that comprise the definitions of extant versions of the MetS.

Insulin Resistance/Hyperinsulinemia and the Components of the MetS

Obesity. If we focus on the relationship between obesity and insulin resistance, three issues must be clarified. Firstly, in contrast to the other criteria proposed to make a diagnosis of the MetS, excess adiposity is not a consequence of insulin resistance, but a change that increases the likelihood that an individual will be insulin resistant. Differences in level of adiposity, *per se,* can explain approximately 25% of the more than six-fold variability in insulin-mediated glucose uptake (IMGU) that exists in an apparently healthy population [9–11].

Secondly, there is a perception that abdominal obesity, as estimated by measuring waist circumference (WC) is uniquely associated with decreases in IMGU, as compared to measures of overall obesity, as estimated by determining body mass index (BMI). In this context it should be realized that measurements of BMI and WC in approximately 15,000 participants in the National Health and Nutrition Examination Survey (NHANES) indicated that the correlation coefficient between the two indices of obesity was greater than 0.9 irrespective of the age, gender, and ethnicity of groups evaluated [12]. Furthermore, the relationships between the two indices of obesity

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(WC and BMI) and a specific measure of IMGU were essentially identical, as were their relative abilities to identify individuals at increased CVD risk [13,14].

Finally, not all obese individuals are insulin resistant [15–19]. As a corollary, risk factors for CVD are confined to the subset of obese individuals that are also insulin resistant [15–19], and prospective studies indicate that obesity, *per se,* in the absence of the metabolic characteristics of insulin resistance, does not increase the incidence of either CVD or type 2 diabetes [20,21].

Glucose Intolerance. The prevalence of some degree of abnormal glucose tolerance and/or type 2 diabetes (2DM) is the abnormality most closely related to insulin resistance. More than 60 years ago. Himsworth and Kerr [22] presented evidence that "a state of diabetes might result from inefficient action of insulin as well as from a lack of insulin," and in 1949 [23] suggested that "we should accustom ourselves to the idea that a primary deficiency of insulin is only one, and then not the commonest, cause of the diabetes syndrome.'

It is now quite clear that resistance to insulin-mediated glucose disposal is present in the great majority of individuals with 2DM [24–28], and that insulin resistance (or hyperinsulinemia as a surrogate estimate of insulin resistance) is a powerful and independent predictor of the development of 2DM [29–32]. Finally, the greater the degree of insulin resistance, the higher the plasma glucose response to oral glucose is in individuals with normal oral glucose tolerance [33]. Thus, there is an enormous amount of evidence documenting a very close relationship between insulin resistance and abnormal elevations in plasma glucose concentration.

Finally, it should be emphasized that nondiabetic individuals with relatively minor degrees of glucose tolerance also have higher blood pressures, and the dyslipidemic changes-a high TG and a low high-density lipoprotein cholesterol (HDL-C) concentration—that comprise the remaining metabolic criteria of all three definitions of the MetS [28,34–36]

Dyslipidemia. It has been known for approximately 40 years that there is a highly significant relationship between insulin resistance, compensatory hyperinsulinemia, and hypertriglyceridemia [37,38]. It is now apparent that the link between insulin resistance/hyperinsulinemia and dyslipidemia is not limited to an increase in plasma TG concentrations. Thus, although the various definitions of the MetS have selected the combination of a high plasma TG and a low HDL-C concentration as diagnostic criteria, it is clear that these changes are also associated with a decrease in low-density lipoprotein (LDL) particle size (small, dense LDL-particles) and the postprandial accumulation of TG-rich remnant lipoproteins [39–41]. Not only are all of these changes significantly associated with insulin resistance/hyperinsulinemia, each *one* has been shown to increase risk of CVD [42–47].

It is necessary to emphasize that each of the constituents of the atherogenic lipoprotein profile described above can develop for reasons *other* than insulin resistance/hyperinsulinemia. On the other hand, insulin resistance/hyperinsulinemia is the only fundamental physiological abnormality that can both account for the clustering of these changes in lipoprotein metabolism, as well as explaining why it occurs more commonly in combination with an elevated plasma glucose concentration and blood pressure.

Blood Pressure. The relationship between blood pressure and insulin resistance/hyperinsulinemia on one hand, as well as that between hypertension and CVD, is more complicated than the relatively simplistic approach to this issue that characterizes all three definitions of the MetS. These issues have been addressed in a recent review article [48], but the following three sets of observations summarize the evidence linking insulin resistance/hyperinsulinemia to essential hypertension.

Firstly, patients with essential hypertension, as a group, are insulin resistant and hyperinsulinemic [49–51]. Secondly, normotensive first-degree relatives of patients with essential hypertension are relatively insulin resistant and hyperinsulinemic as compared to a matched control group without a family history of hypertension [52–54]. Thirdly, hyperinsulinemia, as a surrogate estimate of insulin resistance, has been shown in population-based studies to predict the eventual development of essential hypertension [55–58]. These data provide substantial support that insulin resistance/hyperinsulinemia plays a role in the pathogenesis of essential hypertension.

On the other hand, probably no more than 50% of patients with essential hypertension are insulin resistant [59]. However, it is only this subset of patients that display the components of the various definitions of the MetS that render them at greatest CVD risk. For example, patients with essential hypertension and electrocardiographic evidence of myocardial ischemia are insulin resistant, somewhat glucose intolerant, hyperinsulinemic, and with a high TG and low HDL-C concentration, as compared to either a control group with normal blood pressure, or patients with essential hypertension whose electrocardiograms are entirely normal [60]. The link between the dyslipidemia present in insulin resistant/hyperinsulinemic patients with essential hypertension and CVD is consistent with findings from the Copenhagen Male Study [61] in which $\approx$ 3000 participants were divided into three groups based on their fasting plasma TG and HDL-C concentrations. The results of this prospective study indicated that CVD risk was not increased in patients with essential hypertension with the lowest TG and highest HDL-C concentrations, and that the group at greatest risk was those with a high blood pressure *and* a high TG and low HDL-C concentration, the characteristic dyslipidemia associated with insulin resistance/hyperinsulinemia.

In summary: 1) insulin resistant/hyperinsulinemic individuals are more likely to develop essential hypertension; 2) hypertension is a well-recognized CVD risk factor; 3) patients with essential hypertension *and* a high TG and a low HDL-C are at greatest CVD risk; and 4) the clustering of essential hypertension with glucose intolerance and dyslipidemia can

only be accounted for by accepting a common pathophysiological role for insulin resistance/hyperinsulinemia

Other Contenders for Inclusion into Future Definitions of the MetS. Although current definitions of the MetS do not include these changes, it is pointed out that the components that make up the diagnostic criteria are also associated with a procoagulant and/or proinflammatory state. Although these latter changes have not been elevated to become diagnostic criteria, they are closely associated with insulin resistance. The association between insulin resistance/hyperinsulinemia, elevated concentrations of plasminogen activator inhibitor-1 (PAI-1), and CVD has been known for some time [62,63]. It has also been shown that the increases in PAI-1 concentration seen in insulin resistant, apparently healthy individuals, is accompanied by higher insulin and TG concentrations, and lower concentrations of HDL-C [64]. Thus, variations in PAI-1 concentration cluster with insulin resistance/ compensatory hyperinsulinemia, and the dyslipidemia characteristic of the defect in insulin action.

The proinflammatory factor currently attracting the most attention as indicating increased CVD risk is C-reactive protein (CRP), but there is a much longer history of a relationship between an increase in white blood count (WBC) and heart disease. Indeed, data from the Women's Health Initiative Observational Study suggest that a high WBC was comparable in magnitude as a predictor of CVD risk as increases in CRP concentration [65]. Evidence published several years ago [66] of a relationship between WBC and insulin resistance/compensatory hyperinsulinemia indicated that the WBC in apparently healthy individuals was significantly correlated with degree of insulin resistance ($r=0.50$, $p>0.001$), the magnitude ($p<0.001$) of the plasma glucose ($r=0.48$) and insulin responses ($r=0.50$) to an oral glucose challenge, and higher TG ($r=0.37$) and lower HDL-C ($r=-0.38$) concentrations ($p>0.005$).

Thus, the additional CVD risk factors considered to be present in patients diagnosed as having the MetS are significantly related to both insulin resistance/hyperinsulinemia, as well as the other components of the MetS. As such, they provide additional evidence indicating that insulin resistance/ hyperinsulinemia offers the only coherent explanation to account for how all of these individual variables cluster together in apparently healthy individuals, and increase risk of CVD.

Conclusion

Although insulin resistance and compensatory hyperinsulinemia provide the best available explanation for the clustering of the components that comprise the various definitions of the MetS, a few caveats must be addressed. In the first place, it is possible that there is a more fundamental, and unrecognized abnormality, that precedes the development of insulin resistance. Secondly, not all insulin resistant individuals will display all of the components that comprise the MetS. Thirdly, the suggestion that insulin resistance/hyperinsulinemia offers the best explanation for the clustering of risk factors that comprise the MetS does not mean that any one of the components cannot develop for unrelated reasons. As indicated above, essential hypertension certainly occurs in insulin sensitive individuals, but these patients do not display the other components of the MetS [59,60]. A high fasting plasma TG concentration and can occur [67] in individuals who have a fundamental defect in the catabolism of TG-rich lipoproteins (fat-induced lipemia), and a low HDL-C concentration can exist as a familial defect in lipoprotein metabolism [68]. In both of these cases the changes in lipoprotein metabolism are independent of any defect in insulin action, and the cluster of abnormalities that have been designated as making up the Met do not occur in these situations. The fact that any *one* of the diagnostic criteria of the MetS can develop in insulin sensitive individuals, does not negate the relationship between insulin resistance/hyperinsulinemia and *all* of these abnormalities. Skepticism as to the clinical and/or pedagogical utility of the MetS should not obscure the fact that at the present time the only way to understand why the components that make up this diagnostic category cluster in the same individual is the fact that they are highly correlated with the same defect-insulin resistance and compensatory hyperinsulinemia.

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