Metabolic Syndrome
Pathophysiology and Implications for Management of Cardiovascular Disease

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Case Presentation: E.C. is a 53-year-old postmenopausal female, referred for treatment of hypertension, with a family history of type 2 diabetes, hypertension, and coronary heart disease (CHD). Until learning that her blood pressure was “too high” during a routine physical examination, she felt well, and her postmenopausal symptoms had responded to hormone replacement therapy. She was not overweight (her body mass index [BMI] was 23.7 kg/m²), and the only abnormality on physical examination was a blood pressure of 145/95 RAR. Laboratory results revealed a normal blood count and urinalysis, with the following fasting plasma concentrations of relevant metabolic variables (in mg/dL): glucose 102, triglycerides (TG) 238, low-density lipoprotein cholesterol (LDL-C) 147, and high-density lipoprotein cholesterol (HDL-C) 52.

E.C. is hypertensive and hypertriglyceridemic and at increased risk for CHD. Less obvious is that these metabolic abnormalities are highly likely to be the manifestations of a more fundamental defect—resistance to insulin-mediated glucose disposal and compensatory hyperinsulinemia, changes that greatly increase CHD risk.1,2 The importance of insulin resistance as a CHD risk factor was first explicated in 1998, and the cluster of abnormalities likely to appear as manifestations of the defect in insulin action designated as syndrome X.1 Support for this notion has grown almost as fast as the names used to describe the phenomenon. The Adult Treatment Panel III (ATP III) has recently3 recognized the importance as CHD risk factors of a “constellation of lipid and nonlipid risk factors of metabolic origin,” designated this cluster of abnormalities as “the metabolic syndrome,” and indicated that “this syndrome is closely linked to insulin resistance.” Table 1 lists the criteria the ATP III stipulated be used to diagnose the metabolic syndrome, and a recent report4 has applied these criteria to the database of the Third National Health and Nutrition Examination Survey (NHANES III) and estimated that 1 out of 4 adults living in the United States merits this diagnosis.

The goal of this presentation is to put into perspective the importance of insulin resistance and compensatory hyperinsulinemia in the pathogenesis and clinical course of CHD, as well as the implications of both the ATP III guidelines concerning the diagnosis of the metabolic syndrome.

Does E.C. Have the Metabolic Syndrome? Is She Insulin Resistant?

E.C. meets the ATP III criteria for hypertension and hypertriglyceridemia. Her waist circumference was not measured, but her BMI indicates that she is not overweight, and it is unlikely that her abdominal girth would be >90 cm. Because neither her plasma glucose nor HDL-C cholesterol concentrations were abnormal by the criteria outlined, she does not have the metabolic syndrome. However, not meeting the ATP III criteria does not mean that E.C. is free from the CHD risk associated with being insulin resistant/hyperinsulinemic. Approximately 50% of patients with essential hypertension are insulin resistant/hyperinsulinemic,5 and these individual are the ones most at increased CHD risk.6,7 For example, the results of a recent prospective study showed that the one-third of hypertensive patients with the highest plasma concentration ratio of plasma triglyceride (TG)/HDL-C had the greatest CHD risk.7 The TG/HDL-C concentration ratio was used because the higher the value, the greater the risk of CHD,8 and the more likely the individual is to be insulin resistant/hyperinsulinemic, with the additional abnormalities associated with this defect in insulin action.1,2 It was also shown that hypertensive patients whose TG/HDL-C concentration ratio placed them in the lowest percentile did not have any increased risk of CHD. Therefore, it can be expected that E.C. is at greatly increased CHD risk.

Insulin resistance and the metabolic syndrome are not synonymous. Resistance to insulin-mediated glucose disposal greatly increases the likelihood of developing a cluster of related abnormalities described subsequently. E.C. may not have the metabolic...
syndrome, but she is insulin resistant, and at greatly increased risk to develop type 2 diabetes and CHD, in addition to her hypertension.

**What Is the Relationship of the Five Criteria Selected by the ATP III for Identifying the Metabolic Syndrome to the Presence of Insulin Resistance?**

Abdominal obesity is not a manifestation of insulin resistance, but an anthropometric variable that may accentuate the degree of insulin resistance above that due to the untoward effect of generalized obesity, and the strength of the association between insulin resistance and abdominal obesity, as compared with generalized obesity, is almost certainly exaggerated. Indeed, the relationship between obesity and insulin resistance is also overstated, and the European Group for the Study of Insulin Resistance (EGIR) concluded on the basis of a bi-ethnic study of nondiabetic Pima Indians and Caucasians found that obesity only accounted for 25% of the variability in insulin-mediated glucose disposal in both ethnic groups. Not all overweight subjects are insulin resistant, nor are all insulin-resistant individuals overweight.

The fasting plasma glucose concentration is the variable with the greatest positive predictive value, and a concentration between 110 and 126 mg/dL is highly predictive of insulin resistance/hyperinsulinemia. However, it is not a sensitive indicator, and the vast majority of insulin-resistant/hyperinsulinemic individuals will have a fasting glucose concentration >110 mg/dL. Although hyperinsulinemia, a surrogate measure of insulin resistance, predicts the development of hypertension, no more than 50% of patients with essential hypertension are insulin resistant. If patients with essential hypertension do not meet the criteria for hyperglycemia and dyslipidemia shown in Table 1, it is unlikely that they are insulin resistant/hyperinsulinemic.

The ATP III criteria most likely to identify insulin resistant/hyperinsulinemic individuals are the changes in plasma TG and HDL-C concentrations listed in Table 1. We have examined the relationship between the TG/HDL-C concentration ratio and a specific measure of insulin-mediated glucose disposal in ~400 healthy volunteers and found that that correlation coefficient (r=0.6) was almost identical to that between insulin resistance and fasting plasma insulin concentration (a commonly used surrogate measure of insulin resistance). In addition, the TG/HDL-C concentration ratio provides an independent estimate of CHD risk. Thus, the TG/HDL-C concentration ratio is a powerful predictor of both insulin resistance and CHD risk.

**What Are the Disease-Related Consequences of Insulin Resistance/Compensatory Hyperinsulinemia?**

Insulin-mediated glucose disposal by muscle varies ~10-fold in healthy, nondiabetic, normotensive individuals. The more insulin sensitive the muscle, the less insulin needs to be secreted in order to maintain normal glucose homeostasis. Table 2 presents a list of the changes that are more likely to occur in insulin-resistant individuals able to maintain the degree of compensatory hyperinsulinemia needed to prevent the onset of type 2 diabetes.

In addition to the changes listed in Table 2, there is increasing evidence that nonalcoholic steatohepatitis and several forms of cancer are more likely to occur in insulin-resistant/hyperinsulinemic individuals. Not all insulin-resistant/hyperinsulinemic individuals will develop the entire cluster of abnormalities listed in Table 2, and the number of manifestations present in an insulin-resistant individual will vary with the cut-point used to separate normal from abnormal. In the case of E.C., a glucose concentration of 103 mg/dL, not 110 mg/dL, is why she is not diagnosed with the metabolic syndrome. In addition, none of the abnormalities listed in Table 2 are solely regulated by insulin resistance and/or the plasma concentration ratio provides an independent estimate of CHD risk. Thus, the TG/HDL-C concentration ratio is a powerful predictor of both insulin resistance and CHD risk.
insulin concentration. Two individuals can be equally insulin resistant/hyperinsulinemic, with a comparable increase in hepatic TG secretion, but differ in terms of their ability to remove TG-rich lipoproteins from plasma. As a consequence, one subject will have a TG concentration of 140 mg/dL, as compared with 180 mg/dL in the other. The situation is even more complicated in the case of essential hypertension. The fact that insulin resistance/hyperinsulinemia have nothing to do with the increased blood pressure in ≈50% of patients with this syndrome should not detract from understanding that a substantial proportion of patients with essential hypertension are insulin resistant/hyperinsulinemic and at the highest CHD risk. 

Insulin resistance is not a disease; it is a physiological change that increases the risk of developing one or more of the abnormalities listed in Table 2. The more insulin resistant an individual, and the greater the degree of compensatory hyperinsulinemia, the more likely to develop one or more of the abnormalities listed in Table 2. Conversely, the more abnormalities present, the greater the chances of the individual being insulin resistant. Not all insulin-resistant individuals develop these abnormalities, nor is their appearance confined to insulin-resistant individuals. On the other hand, the presence of any one of them indicates that the individual may be insulin resistant and increases the possibility that the other abnormalities may also be present.

What Is the Clinical Utility of Diagnosing the Metabolic Syndrome?

The greatest benefit of the ATP III approach to diagnosis of the metabolic syndrome is the recognition that CHD risk is not limited to hypercholesterolemia, and that insulin resistance/hyperinsulinemia and the consequences stemming from these defects in insulin metabolism must be considered in efforts aimed at decreasing CHD risk. The greatest danger is that use of the ATP III criteria will direct attention away from the information in Table 2 to focus on whether or not a patient has the metabolic syndrome. The conceptual importance of the metabolic syndrome is to indicate that the abnormalities listed in Table 2 are more likely to occur together than separately, and when they cluster, they are almost certainly related to insulin resistance/hyperinsulinemia. The more attention paid to the concept of the metabolic syndrome, rather than to a specific set of arbitrary criteria, the more likely that appropriate therapeutic decisions will be made. Thus, although many of the changes listed in Table 2 are not measured routinely, there is substantial evidence that they are all CHD risks, and their association with insulin resistance/hyperinsulinemia makes it essential that therapeutic efforts take this relationship into consideration.

Therapeutic implications of the metabolic syndrome are self-evident. Excess adiposity and physical inactivity are the major lifestyle variables that have an untoward effect on insulin action. Thus, once it seems likely that insulin resistance is present, and leading to the abnormalities listed in Table 2, weight loss and increased physical activity, when appropriately initiated, will enhance insulin sensitivity and decrease the associated CHD risk factors. The therapeutic approach to E.C. will also vary as a function of how the relationship between her clinical presentation and insulin resistance is perceived. She is hypertensive and hypercholesterolememic, but does not meet the ATP criteria for the metabolic syndrome. If this is interpreted as meaning she is insulin sensitive, it is likely that she will be placed on a low fat–high carbohydrate diet, drug treatment of her hypertension initiated, and pharmacological treatment of her hypercholesterolemia considered after a period of dietary intervention. However, if she is perceived as being insulin resistant, it will be realized that the prescribed diet will accentuate her hyperinsulinemia, leading to a higher TG concentration, enhanced postprandial lipemia, smaller and denser LDL particles, and a lower HDL-C concentration. Thus, failure to focus on the central role played by insulin resistance in this instance has led to an intervention that has increased, not decreased, CHD risk.

Conclusion

Insulin resistance and its cluster of associated abnormalities are probably as important as hypercholesterolemia as CHD risk factors. The report of the ATP III serves as a formal recognition of this fact, and the notion that ≈25% of the US population may be suffering from the untoward consequences of insulin resistance emphasizes the magnitude of the clinical problem. Given this information, efforts to reduce CHD must take into account the importance of the series of related abnormalities listed in Table 2, and that new therapeutic approaches be evaluated that recognize that there is more to CHD than hypercholesterolemia.

References

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