Beyond Type 2 Diabetes: The Need for a Clinically Useful Way to Identify Insulin Resistance

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As the health burden of obesity and a sedentary lifestyle increases, more efforts are required to identify persons who are at risk of complications. For example, type 2 diabetes now accounts for over $98 billion in health care costs (1) and excess cardiovascular disease mortality. It can, however, be prevented by lifestyle interventions. In the Finnish Diabetes Prevention Study (2) and the Diabetes Prevention Program (3), weight loss and moderate exercise reduced the relative risk of developing diabetes by 58% during 3 years among overweight men and women with impaired glucose tolerance. Furthermore, it is well established that the vast majority of patients who eventually develop type 2 diabetes are insulin resistant, and that frank hyperglycemia occurs when these patients can no longer sustain the degree of compensatory hyperinsulinemia required to prevent gross decompensation of glucose homeostasis.

In addition to increasing the risk of type 2 diabetes by eightfold, insulin resistance is associated with a twofold increase in the risk of hypertension and a threefold risk of coronary heart disease (4). It is also a major component in other conditions such as polycystic ovarian syndrome and nonalcoholic fatty liver disease. Because approximately 50% of the variability of insulin-mediated glucose disposal can be explained by differences in the degree of adiposity and level of physical fitness (5), the clinical effect of insulin resistance can be expected to increase as the U.S. population becomes heavier and less fit. Thus, it is important to identify apparently healthy persons who are already sufficiently insulin resistant to be at increased risk of developing adverse outcomes due to this defect in insulin action.

Although there are methods for quantifying insulin-mediated glucose disposal directly, they are not easily applied in clinical practice or large-scale epidemiological studies. Thus, much of the evidence evaluating the relation between insulin resistance and various clinical syndromes is based on the observation in nondiabetic persons that insulin resistance is associated with elevations in plasma insulin concentration (6). This relation between insulin resistance and compensatory hyperinsulinemia has formed the basis of several surrogate estimates of insulin resistance using various measurements of plasma insulin concentration. In this issue of *The American Journal of Medicine*, Pradhan and colleagues (7) have shown that fasting levels of plasma insulin and proinsulin, and the concentration ratio of fasting proinsulin/insulin, were associated with a 5.6- to 16.4-fold increase in the risk of type 2 diabetes. The current report supports the findings of several earlier studies (4,8,9), demonstrating that insulin resistance or compensatory hyperinsulinemia predicts the development of type 2 diabetes, and extends these findings to a population of healthy middle-aged women. The authors' suggestion that fasting hyperinsulinemia signifies insulin resistance and a high proinsulin: insulin ratio indicates an incipient decline in insulin secretory function is not as self evident, however, and the utility of the proinsulin:insulin ratio as a marker of insulin secretory function remains to be validated.

Although the pathophysiological interpretation of the importance of these surrogate markers can be debated, the authors' observation that markers of insulin resistance can predict the development of type 2 diabetes in apparently healthy women is of considerable interest in light of the multiple adverse consequences associated with this fundamental abnormality. In the study, differences between the women who developed diabetes during the follow-up and controls were not limited to insulin level; the cohort that developed diabetes was also heavier; more likely to have a family history of diabetes, hypertension, and dyslipidemia; and exercised and used alcohol less frequently. Thus, factors previously shown to be associated with a greater degree of insulin resistance were present in these women. The results of this study, as well as of many others, have provided relatively simple clinical tools to identify persons who are sufficiently insulin resistant to be at increased risk of developing not only type 2 diabetes but also other adverse outcomes associated with impaired insulin action. Although clinical markers of insulin resistance have been shown to predict adverse events (10), fasting insulin has also been shown to predict cardiovascular events and mortality, as well as overall mortality. In the Kuopio Ischaemic Heart Disease Risk Factor Study (11), hyperinsulinemia and obesity, hypertension, or dyslipidemia was associated with about a threefold increased risk of cardiovascular disease mortality and about a twofold increased risk of all-cause mortality. Similarly, a nested case-control study within the Quebec Cardiovascular Study cohort showed that among those who developed a first ischemic event (12), fasting plasma insulin levels were 18% higher ($P < 0.001$) than in

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controls matched for age, body mass index, smoking, and alcohol consumption. This association persisted after adjustment for plasma triglyceride, apolipoprotein B, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol concentrations.

Although it is clear that plasma insulin concentrations might serve as a potential diagnostic tool to identify persons at high risk of adverse clinical outcomes, the use of this assay is severely limited at this time because of a lack of standardization. The results in this paper do emphasize the need to overcome this problem and to accelerate efforts to move insulin measurements from the research laboratory to the clinical arena. As emphasized earlier, lifestyle interventions that enhance insulin sensitivity have been shown to decrease the rate of progression to type 2 diabetes effectively (2,3). Thus, it seems reasonable that the availability of a standardized method to measure plasma insulin concentrations would be of great benefit in preventing diseases related to a condition that may be silent but that is now well recognized to be both widely prevalent and responsible for considerable morbidity and mortality—insulin resistance.

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