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Insulin Resistance, Type 2 Diabetes Mellitus, and Cardiovascular Disease The End of the Beginning

Gerald Reaven, MD

In his 1939 Goulstonian Lectures to the Royal College of Physicians in London, Harold Himsworth addressed the “Mechanisms of Diabetes.” In the course of these 3 presentations,^{1–3} he provided evidence that “diabetes mellitus is a disease in which the essential lesion is a diminished ability of the tissue to utilize glucose. The high blood sugar is a controlled and compensatory phenomenon, the object of which is to facilitate the utilization of glucose by the tissues.” In addition, he challenged the conventional wisdom that “all causes of human diabetes could be explained by deficiency of insulin” and went on to utter the heretical notion that “a state of diabetes might result from inefficient action of insulin as well as from a lack of insulin.” Thus, the notion of a causal role of insulin resistance in human disease was born almost 70 years ago.

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Despite the fact that Himsworth was among the most distinguished clinical investigators of his time and in 1949 concluded in the Oliver-Shapley Lectures to the Royal College of Physicians⁴ “that it appears we should accustom ourselves to the idea that primary deficiency of insulin is only one, and then not the commonest cause of the diabetes syndrome,” the idea that resistance to insulin action could have adverse consequences had little resonance over the next several decades. However, this situation began changing rapidly with the introduction of methods to quantify insulin-mediated glucose disposal,^{5,6} and it soon became clear^{7,8} that the majority of patients with type 2 diabetes mellitus were, in Himsworth’s terms, “insulin insensitive.” Subsequent prospective studies were published demonstrating that insulin resistance and/or compensatory hyperinsulinemia as a surrogate estimate of insulin resistance predicted the development of type 2 diabetes mellitus,^{9,10} providing the final evidence of the prescience of Himsworth’s mechanistic concept of the clinical syndrome of diabetes mellitus.

At approximately the same time that the importance of insulin resistance in the etiology of type 2 diabetes mellitus was becoming widely acknowledged, it seemed important to

point out that frank hyperglycemia only developed in a relatively small proportion of individuals with that defect in insulin action.¹¹ Instead, the majority of insulin-resistant individuals continue to secrete enough insulin to maintain normal or near-normal glucose tolerance. However, this philanthropic response on the part of the pancreatic beta cell was not without cost, and insulin-resistant/hyperinsulinemic individuals were more likely to have some degree of glucose intolerance, a high plasma triglyceride and low HDL cholesterol concentration, and elevated blood pressure.¹¹ Because these changes increase cardiovascular disease (CVD) risk,^{12–15} insulin resistance/hyperinsulinemia, owing to its associated abnormalities, contributed substantially to CVD. To emphasize that insulin-resistant persons were at increased risk to develop both type 2 diabetes mellitus and CVD, the term “syndrome X” was introduced as a conceptual way to understand why a defect in insulin action could increase CVD in nondiabetic individuals.

Considerable information has accumulated since the suggestion that a cluster of abnormalities related to insulin resistance/hyperinsulinemia increased CVD risk, and we now know that many more CVD risk factors are present in insulin-resistant, nondiabetic individuals. More recently, the elements that composed the physiological concept of syndrome X have been used as criteria with which to make a diagnosis of the metabolic syndrome, as defined in the report of the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program.¹⁶ Although 4 of the criteria proposed by the ATP III to diagnose the metabolic syndrome—glucose intolerance, a high triglyceride and low HDL cholesterol, and elevated blood pressure—parallel the abnormalities that comprise syndrome X,^{8,11} there are 2 important differences between the 2 concepts. At the simplest level, obesity is not a component of syndrome X, because in contrast to the other variables, it is not a consequence of insulin resistance but only increases the likelihood of an individual becoming insulin resistant and developing the associated adverse consequences.¹⁷ This point of view receives support from the results of the recent study by Ninomiya et al¹⁸ showing that abdominal obesity, as defined by the ATP III, was the only 1 of their 5 variables not statistically associated with the development of either CVD or stroke in an analysis of the data from the Third National Health and Nutrition Examination Survey (NHANES III). The authors suggested that this finding “may reflect an indirect effect of high WC [waist circumference] through other components of the syndrome.” In the same vein, physical inactivity acts similarly to obesity in increasing the

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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likelihood that insulin resistance will develop, and results of prospective studies have shown that physical inactivity seems to be as potent as obesity, if not more so, in increasing risk of developing type 2 diabetes mellitus or CVD.^{19,20}

At a more fundamental level, syndrome X was an effort to provide a physiological construct to explain how a defect in insulin action can lead not only to type 2 diabetes mellitus but also to CVD. In contrast, the metabolic syndrome as defined by the ATP III is a clinical diagnosis, satisfied by fulfilling 3 of the 5 criteria proposed. The clinical utility of making a diagnosis of the metabolic syndrome, or more importantly, the potential disservice to an individual who might only satisfy the triglyceride and blood pressure criteria and therefore not be “diagnosed” as having the metabolic syndrome, is an important issue and one that requires attention. For example, Ninomiya et al¹⁸ indicated that these 2 criteria were the most predictive of an individual developing either CVD or stroke. Would the clinical approach differ if such an individual did not satisfy a third ATP III criterion?

The publication by Wilson et al²¹ in the present issue of *Circulation* provides clear evidence that insulin resistance and its cluster of associated abnormalities (metabolic syndrome) increases the risk of type 2 diabetes mellitus and CVD. Additionally, their findings demonstrate that the cluster of abnormalities related to insulin resistance are more powerful predictors of type 2 diabetes mellitus than CVD, presumably because there certainly are CVD risk factors unrelated to insulin resistance, eg, an elevated LDL cholesterol concentration. They also point out that the ability to predict type 2 diabetes mellitus and CVD is not dependent on satisfying 3 of the 5 ATP III criteria, and 2 seemed to do as well as 3. This latter finding they consider consistent with the “hypothesis that even a modest degree of risk factor clustering reflects a global underlying insulin resistant pathophysiology, and individual risk factors may contribute marginally to the insulin resistant phenotype.” This conclusion is reminiscent of the comments by Ninomiya and associates,¹⁹ as is the finding that the 2 best predictors of adverse CVD outcomes in the study by Wilson et al²¹ were elevated blood pressure and a low HDL cholesterol concentration. Not surprisingly, Wilson et al²¹ also point out that the best predictor of type 2 diabetes mellitus is the fasting plasma glucose concentration.

In addition to pointing out that 2 abnormalities may be as effective as 3 in determining an adverse outcome and that the clinical impact will vary as a function of which specific abnormalities are present, Wilson et al²¹ also emphasize that the prevalence of the ATP III criteria varies widely. These observations are important in that they support the view that it is more clinically relevant in a given patient to determine whether any of the conveniently measured abnormalities related to insulin resistance exist and which of them is present, rather than whether or not the 3 criteria needed to make a diagnosis of the metabolic syndrome are satisfied. Indeed, this appears to be the conclusion recently reached in the joint position paper issued by the American Diabetes Association and the European Association for the Study of Diabetes.²² In this report, they conclude the following: (1) “providers should avoid labeling patients with the term

metabolic syndrome”; (2) “adults with any major CVD risk factor should be evaluated for the presence of other CVD risk factors”; and (3) “all CVD risk factors should be individually and aggressively treated.”

Although the findings by Wilson and colleagues²¹ should serve to end questions concerning the importance of insulin resistance and its consequences with regard to increasing risk of type 2 diabetes mellitus and CVD, the story of the role of insulin resistance in human disease, begun by Himsworth, is far from over. Type 2 diabetes mellitus and CVD are not the only clinical syndromes associated with insulin resistance and its consequences. For example, there is substantial evidence that several clinical syndromes are more likely to occur in insulin-resistant/hyperinsulinemic persons,²³ including polycystic ovary syndrome, nonalcoholic fatty liver disease, certain forms of cancer, and sleep-disordered breathing. Furthermore, the appearance of insulin resistance and its consequences complicates drug treatment of patients with HIV infection²⁴ and schizophrenia²⁵ and possibly contributes to the development of various neurodegenerative disorders.²⁶

In conclusion, Wilson and colleagues²¹ have evaluated the ability of the ATP III criteria for diagnosing the metabolic syndrome to predict the development of type 2 diabetes mellitus and CVD. The ATP III is not the only organization that has apparently felt the need to propose criteria with which to diagnose the metabolic syndrome. Rather than discussing the pros and cons of the various definitions, I believe it more useful to cease debating their relative benefits, focusing in the future on addressing the many unresolved issues concerning the role of insulin resistance and associated abnormalities in human disease. Although it is an outrageous example of hyperbole to mention the report by Wilson and colleagues²¹ in the same paragraph as the Battle of El Alamein, the following words of Churchill to the English Parliament after that victory may be the most appropriate way to mark this moment in our perception of the role of insulin resistance in human disease—a doorway opened by Himsworth nearly 70 years ago: “Now, this is not the end, it is not even the beginning of the end, but it is, perhaps the end of the beginning.”

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