Consensus Development Conference on Insulin Resistance

5–6 November 1997

AMERICAN DIABETES ASSOCIATION

The possibility that there can be defects in the sensitivity of tissues to insulin action in people with diabetes was first reported nearly 50 years ago (1). Since then many investigators have described, with increasing detail, the pathogenesis and consequences of what has become known as "insulin resistance."

As our understanding of the biology of glucose homeostasis has grown, insulin resistance has clearly emerged as an important cause of glucose intolerance leading to type 2 diabetes, and may even play a role in other pathological conditions. Type 2 diabetes is a heterogeneous disorder, requiring impairment of both insulin secretion and insulin action (insulin resistance). Medical nutrition therapy (MNT) and exercise therapy, as well as a number of pharmacological interventions, have demonstrated that reducing insulin resistance will improve glucose homeostasis.

Despite the wealth of knowledge that characterizes the nature of insulin resistance (namely, its impact on health role in disease, its biochemical basis, and its measurement) many fundamental questions remain. To assess our present knowledge and understanding and to provide guidance to practitioners, the American Diabetes Association convened a Consensus Development Conference 5–6 November 1997, on the subject of insulin resistance.

A six-member panel heard presentations from 19 experts, complemented by audience participation, on three broad topics related to insulin resistance: its definition and measurement, its cause(s), and its clinical implications and pathophysiological consequences. The panel then developed a consensus position on the following five questions:

1. What is the definition of insulin resistance and how should it be measured?
2. What is the mechanism(s) of insulin resistance?
3. Does insulin resistance predict diabetes? Is it a risk factor for cardiovascular disease?
4. Should insulin resistance be treated for the primary prevention of diabetes or other diseases?
5. Should insulin resistance be treated for the secondary prevention of the complications of diabetes or other diseases?

QUESTION 1: What is the definition of insulin resistance and how should it be measured?

Historically, Himsworth and Kerr (1) used the term insulin insensitivity (synonymous with insulin resistance) to define the relatively poor glucose response to exogenous insulin exhibited by obese diabetic patients. The radioimmunoassay of insulin, first available in 1960, afforded a quantitative comparison of circulating insulin and glucose concentrations. This major advance was used to demonstrate that absolute insulin levels could be elevated in the presence of type 2 diabetes. Studies in the mid-1960s showed that obesity is associated with hyperinsulinemia, leading to the revival of an older concept that obesity→ insulin resistance→ islet cell failure or exhaustion (type 2 diabetes). The concept that absolute hyperinsulinemia, regardless of body habitus, might also represent a prediabetic state, has recently regained currency.

Insulin resistance is defined as an impaired biological response to either exogenous or endogenous insulin. The measured biological responses could reflect, in theory, metabolic processes (changes in carbohydrate, lipid or protein metabolism) as well as mitogenic processes (alterations in growth, differentiation, DNA synthesis, regulation of gene transcription). In vivo biological responses to insulin vary according to insulin concentration, exposure time, tissue delivery, and pulsatility.

Even though the glucose-insulin relationship is clinically pertinent, it is also important to recognize that, conceptually, insulin resistance does not have to be confined just to parameters of glucose metabolism. The concept of insulin resistance should apply to any of the biological actions of insulin, and might include its effects on lipid and protein metabolism, vascular endothelial function, and gene expression.

The term insulin resistance should not be confused with the concept of the "insulin resistance syndrome" (or syndrome X [2]). The latter is a constellation of associated clinical and laboratory findings, consisting of glucose intolerance, central obesity, dyslipidemia (increased triglycerides, decreased HDL, increased small dense LDL), hypertension, increased prothrombotic and antifibrinolytic factors, and a predilection for atherosclerostic vascular disease. There are a number of other insulin-resistant conditions with specific clinical presentations (e.g., polycystic ovarian syndrome [PCOS], pregnancy, glucocorticoid therapy) that may not include all the features of the insulin resistance syndrome.

The response to insulin has been measured by a number of different methods (see below). And insulin resistance has been quantified by a number of different indices. Unfortunately, however, there is no universally accepted, clinically useful, numeric expression that defines insulin resistance.

Measurement of insulin resistance

A variety of procedures have been developed to detect the presence of insulin resistance. Among these, three measures have been given the most attention: the euglycemic insulin clamp, the minimal model,

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Abbreviations: CVD, cardiovascular disease; DPP, Diabetes Prevention Program; IRS, insulin receptor substrate; PCOS, polycystic ovarian syndrome.

and the fasting insulin level. Using any of these techniques, there is a wide range of insulin sensitivity in normal individuals, some of whose values overlap with similar values in people with diabetes. Therefore, it is difficult to distinguish between nondiabetic and diabetic individuals on the basis of measures of insulin resistance.

The most widely accepted research method or 'gold standard' is the euglycemic insulin clamp technique originally developed by Andres and coworkers (3,4). With this procedure, exogenous insulin is infused, so as to maintain a constant plasma insulin level above fasting, while glucose is fixed at a basal level by infusing glucose at varying rates. This glucose infusion is delivered via an indwelling catheter at a rate based on plasma glucose measurements every 5 min. When the plasma glucose level falls below basal, the glucose infusion rate is increased to return plasma glucose to basal levels and vice versa. The total amount of glucose infused over time (*M* value) is an index of insulin action on glucose metabolism. The more glucose that has to be infused per unit time, then the more sensitive the patient is to insulin. Conversely, the insulin-resistant patient requires much less glucose to maintain basal plasma glucose levels. The advantage of this test is that the effect of insulin on fuel metabolism can be assessed in the absence of the confounding effects of hypoglycemic counterregulation, endogenous insulin secretion, or variable levels of hyperglycemia. Another advantage is that multiple insulin actions can be assessed by using isotopes, including regulation of glucose uptake and production, inhibition of lipolysis, and changes in protein metabolism.

The clamp technique has, however, a number of limitations. To assess the full spectrum of insulin resistance, several doses of insulin may be needed, and a steady state must be achieved for each dose. The test does not reproduce physiological conditions, in which both plasma glucose and insulin change. Most importantly, the complexity and cost of the procedure limits its use to research laboratories, in which scientific questions can be addressed in limited numbers of subjects. In short, the clamp procedure cannot be adapted to the assessment of insulin resistance in the clinical setting.

In an attempt to develop a more practical method of measuring insulin resistance that could be applied to larger populations, Bergman et al. (5) developed the minimal model. With this procedure, glucose and insulin are sampled frequently from an indwelling catheter during an intravenous glucose tolerance test; the results are entered into a computer model, which generates a value that is an index of insulin sensitivity (called S_i). The acute insulin release (AIR) in response to glucose is also determined by the test. In general, this measure of insulin resistance correlates reasonably well with the euglycemic insulin clamp in nondiabetic subjects. Its accuracy deteriorates in diabetes, however, because the immediate plasma insulin response to the glucose challenge, a major determinant of the analysis, is diminished. Therefore, additional maneuvers are needed to raise plasma insulin levels, such as giving tolbutamide or exogenous insulin in the course of the test. The procedure focuses on glucose, and not other insulin-sensitive fuels and only looks at net effects on glucose metabolism. The individual roles of peripheral and hepatic glucose metabolism are not separated. Moreover, test results are more variable than seen in the clamp technique. On the other hand, the test is simpler, has provided valuable epidemiological data, and does provide information on both insulin action and secretion. Recent analyses suggest that by taking into account both insulin sensitivity and secretion, the predictive value of the minimal model for the development of type 2 diabetes is increased. While this test is useful to a broader number of scientists, it is still not suitable for the clinical setting. This is because of the complexity of the sampling procedure, the several hours of time involved, the sophisticated data analysis, and the cost of the test.

From a clinical perspective, the most practical way of assessing insulin resistance would seem to be the measurement of insulin concentration in plasma. Less is known about the utility of using C-peptide levels, although data thus far show no additional advantage. The measurement of insulin concentration is best done in the overnight fasted condition, since in the postprandial state, glucose levels are changing rapidly and the variable levels of glucose confound the simultaneous measure of insulin levels as an index of insulin action. There is a significant correlation between fasting insulin levels and insulin action as measured by the clamp technique. Moreover, it is generally true that very high plasma insulin values in the setting of normal glucose levels are very likely to reflect insulin resistance, and high insulin levels are a predictor of the development of diabetes. As individuals develop diabetes, plasma glucose increases and plasma insulin decreases. As a result, the plasma insulin level no longer reflects only insulin resistance because it becomes influenced by the appearance of a β-cell defect and hyperglycemia.

The value of the measurement of fasting insulin is also limited by the fact that there is considerable overlap between insulin resistant and normal subjects. Another major limitation is the lack of standardization of the insulin assay procedure. A report of the ADA Task Force on Standardization of the Insulin Assay (6) concluded that replicate patient samples measured in different laboratories showed a high degree of variability which was not corrected by a single reference standard. Although assays vary depending on their ability to detect proinsulin and its conversion intermediates, there were unexplained differences between laboratories even when they used the same standard to determine insulin concentrations. As a result, the task force recommended the establishment of a central laboratory that would certify the performance of insulin assays in the clinical setting. Such a centrally administered program, while essential, has yet to be established.

If the assay for fasting insulin was reliable, it would be useful to detect insulin resistance early (i.e., before or soon after the pubertal period, which itself causes insulin resistance) and before clinical disease appears. However, we do not recommend routine screening of patients using fasting insulin measurements because of the following liabilities: the problems with assay procedures, the inability of the measurement to accurately indicate the presence of insulin resistance, the lack of a well-defined cutpoint differentiating normal from abnormal, and the lack of data establishing whether modification of insulin resistance has an impact on outcomes.

QUESTION 2: What is the mechanism(s) of insulin resistance?

Understanding the biology of insulin resistance is important to identify affected causative genes and their products, to facilitate the development of new therapies, and to optimize current therapies. The aspect of insulin resistance, which has been most extensively studied in man, animal models of diabetes, and cell culture, is the defective insulin-mediated uptake and uti-

lization of glucose. In patients with insulin resistance, this defect is manifested by a reduction in insulin-stimulated storage of glucose as glycogen in muscle and liver. In muscle, the primary mechanism responsible appears to be a block in the glucose transport/phosphorylation step. This defect has both a primary genetic component and a secondary environmental component.

The primary genetic component is characterized by reduced efficiency of translocation of the GLUT4 in muscle cells, although nuclear magnetic resonance (NMR) data in humans suggest that a separate defect in glycogen synthesis may also exist. In cell culture, several lines of evidence suggest that the phosphatidylinositol kinase (PI 3-kinase) pathway, one of the two major pathways activated by insulin receptor phosphorylation of insulin receptor substrate (IRS)-1, is both necessary and sufficient for stimulating GLUT4 translocation. In another model, knockout mice, heterozygous for either the insulin receptor or for IRS-1, are not insulin resistant, yet mice heterozygous for both the insulin receptor and for IRS-1 are insulin resistant. These observations suggest that a critical threshold level of IRS-1 activity is necessary in order to maximally stimulate PI-3 kinase, and further suggest that IRS-1 may play a central role in insulin-stimulated GLUT4 translocation in the intact animal. Other experiments with knock-out mice suggest that insulin resistance can be abolished by blocking the action of endogenous tumor necrosis factor-α (TNF-α). It is likely that the molecular basis of insulin resistance is polygenic, and the relative contribution of individual components may vary among individuals. The additive effects of several mild alterations of signal transduction pathway molecules may be sufficient to induce insulin resistance.

The environmental component of insulin resistance involves the effects of increased levels of glucose and free fatty acids. The effects of chronic hyperglycemia, termed "glucotoxicity," reduce insulin-stimulated glucose uptake by decreasing GLUT4 translocation in muscle. Two possible mechanisms have been investigated. One involves increased glucose flux through the glucosamine pathway. This pathway may induce insulin resistance in muscle when metabolite flux exceeds demand, so that the metabolites may be shunted to the liver for conversion to fat. Hyperglycemia may also activate isoforms of protein kinase C, which in turn may increase serine phosphorylation, decrease activity of the insulin receptor and/or IRS-1, and thereby decrease their activity. Elevated plasma levels of free fatty acids also can increase insulin resistance by decreasing glucose transport and phosphorylation in muscle perhaps by acylating regulatory proteins, or by giving rise to diacylglycerol, which activates protein kinase C. The capacity of free fatty acids to inhibit glycolysis also plays a role in insulin resistance.

The above summary only briefly touches on our knowledge of intracellular signaling mechanisms and their role in insulin-mediated glucose uptake and storage. We still, however, need much more information before insulin resistance is completely understood at the molecular level.

QUESTION 3: Does insulin resistance predict diabetes? Is it a risk factor for cardiovascular disease?

Plasma insulin levels whether measured in the fasting state or after a glucose load are a powerful predictor for the risk of type 2 diabetes, independent of obesity or waist circumference. This risk is particularly strong for individuals with a family history of diabetes. It is not known whether the risk relationship is linear or curvilinear, and the risk gradient is unknown. The insulin sensitivity index and the acute insulin response are also both very strong predictors of the risk of diabetes.

It is likely that measures of insulin sensitivity and acute insulin responses are better predictors of the risk of diabetes than is a fasting insulin level, although it is not known how much better they are. Given the cost and complexity of specific testing for insulin sensitivity, including the simpler approaches previously described, the predictability of these tests for the development of diabetes would have to be substantially better than that of a fasting insulin level in order for them to be clinically useful. At present, the comparative predictability of the fasting insulin level versus the various insulin sensitivity indexes has not been determined in any randomly selected population sample followed for a long period of time. However, by using existing data sets we may be able to compare the predictability of diabetes by various methods of measuring insulin resistance. Also, by more accurately defining the laboratory phenotypes of insulin resistance we may improve the success of identifying genes related to insulin resistance.

The identification of insulin resistance at an early age may be especially beneficial for the offspring of type 2 diabetic patients. Thus, more complex testing of insulin sensitivity, such as using the minimal model, may be useful in high-risk families (7). The application of such testing would require further simplification and standardization of the methods, and the availability of facilities to do such testing.

There is no question that diabetes is associated with a substantial increased risk of cardiovascular disease (CVD) and greater morbidity and mortality from cardiovascular events. It is also likely that insulin resistance is related to the risk of CVD. Although there are populations that have a high prevalence of diabetes and insulin resistance, without an increase in the incidence of coronary heart disease, such populations are generally characterized as having low cholesterol and saturated fat consumption, and low LDL levels. This is generally not the case in the U.S. Therefore, in the U.S., insulin resistance probably combines with dyslipidemia in contributing to greater risk of CVD.

The risk of CVD associated with a single measure of fasting insulin is affected by the variability of the insulin measurement, and the association of insulin resistance with other cardiovascular risk factors (e.g., low HDL, hypertension, central obesity, high triglyceride levels). Adjustment for all these other factors in multivariate analyses may not always clarify the independent role of insulin resistance. Therefore, a single measure of a fasting insulin is not a good predictor of the risk of CVD and should not be routinely used as a measure of cardiovascular risk.

QUESTION 4: Should insulin resistance be treated for the primary prevention of diabetes or other diseases?

The fact that insulin resistance is associated with so much morbidity and mortality does not prove that it is the cause of these outcomes, or that amelioration of insulin resistance will prevent them. Furthermore, lacking a clinically practical test for insulin resistance or a way to follow it longitudinally in the clinical setting, it is impossible for the clinician to know whether a given

treatment is specifically alleviating insulin resistance and preventing its associated conditions.

Nevertheless, there are a series of interventions that do reduce insulin resistance, including hypocaloric diet, weight reduction, exercise, and the medications metformin and troglitazone. The effect of a low-calorie diet on insulin resistance has been known for many years. Insulin resistance is reduced within a few days of instituting a hypocaloric diet, even before much weight loss has occurred. Weight reduction, attained over a longer time frame, further improves insulin sensitivity. Conversely, avoiding excess weight gain may be the most effective means to prevent insulin resistance and its associated morbidity. Distribution of dietary calories among carbohydrates and various fat sources does not appear to be so critical in influencing insulin resistance as is total caloric intake (i.e., to establish a hypocaloric diet). Reduction of saturated fat intake is important in improving a high-risk lipid profile.

The effects of exercise are complex. Regular vigorous exercise improves $V_{O_{2max}}$ and reduces insulin resistance, even in the elderly. This training effect on insulin resistance drops off quickly, within 5 days after cessation of the exercise. Long-term exercise results in little weight reduction unless caloric intake is controlled. However, a cardiovascular benefit may be obtained with even modest levels of habitual exercise.

There are two relatively specific pharmacological approaches to reducing insulin resistance. Metformin enhances insulin's suppression of hepatic glucose output, and has modest effects on peripheral glucose utilization. Troglitazone is an insulin sensitizer, acting by enhancing insulin-stimulated peripheral glucose disposal. Both drugs are now available in the U.S. for the treatment of type 2 diabetes, but neither is currently approved to treat insulin resistance in the absence of diabetes.

While lifestyle changes and pharmacological approaches do reduce insulin resistance and may put people in a lower risk category for diseases associated with insulin resistance, there is little evidence that morbidity is actually prevented. The most direct link of insulin resistance to morbidity and mortality is by way of type 2 diabetes (6). People with insulin resistance, measured rigorously by the euglycemic insulin clamp or the minimal model are at greatly increased risk of developing impaired glucose tolerance and type 2 diabetes. Since the pathophysiology of type 2 diabetes virtually always includes significant insulin resistance, there is good reason to hypothesize that the treatment of insulin resistance could prevent or delay the onset of type 2 diabetes.

A major National Institutes of Health study, the Diabetes Prevention Program (DPP), is designed to determine which, if any, of these treatments is most effective in the primary prevention of type 2 diabetes in people with impaired glucose tolerance, over a 5-year period. A control group and three treatment arms are being studied: intensive lifestyle changes designed to effect a 7% reduction in body weight through caloric reduction and exercise, or the use of troglitazone or metformin. Each of the treatments could be considered to be reducing insulin resistance.

Pending the outcome of the DPP, it is reasonable for the clinician to offer nonpharmacological treatments designed to reduce insulin resistance in the hope of preventing diabetes, recognizing that it will be impossible to prove or disprove efficacy in the individual patient. People at risk include those who are overweight, particularly with central obesity, those with a strong family history of diabetes, a history of gestational diabetes, impaired fasting plasma glucose (i.e., between 110 and 125 mg/dl), or other reasons to suspect insulin resistance (e.g., hypertension and dyslipidemia). Given our current state of knowledge, and until we have the results of the DPP, troglitazone and metformin are not recommended for the prevention of type 2 diabetes.

PCOS causes significant physical and psychological side effects, and almost always includes insulin resistance. Evidence suggests that the hyperandrogenism of PCOS may be caused by hyperinsulinism, and that the hyperandrogenism also contributes to the insulin resistance in women. Although it is not feasible to prevent PCOS, reducing insulin resistance has been reported in small studies to alleviate some of its manifestations.

It is unclear whether insulin resistance causes or is simply associated with many frequently accompanying other high-risk conditions such as hypertension, dyslipidemia, and accelerated atherosclerosis. Given the lack of definitive information on causality, there is inadequate rationale for the pharmacological treatment of insulin resistance itself in the hope of preventing any of these disorders.

QUESTION 5: Should insulin resistance be treated for the secondary prevention of the complications of diabetes or other diseases?

The secondary complications of diabetes can be divided into the cluster of retinopathy, nephropathy, and neuropathy, and a cluster of cardiovascular, cerebrovascular, and peripheral vascular diseases, so-called macrovascular disease.

There is no evidence that insulin resistance, independent of hyperglycemia, has a role in the causation of retinopathy, nephropathy, or neuropathy. Rather, the preponderance of evidence strongly incriminates hyperglycemia in the pathogenesis of these complications. Hence, only to the extent that reducing insulin resistance will significantly lower plasma glucose levels in people with type 2 diabetes, would such a reduction in insulin resistance be useful in preventing retinopathy, nephropathy, or neuropathy. From that perspective, diet, weight reduction, exercise, and all currently available glucose-lowering pharmacological agents, including exogenous insulin itself, should be beneficial to patients with type 2 diabetes if they ameliorate hyperglycemia. All these agents also decrease that portion of insulin resistance that is secondary to "glucose toxicity."

The role of insulin resistance is more complex when considering the macrovascular complications of diabetes. Some evidence suggests that insulin resistance itself, independent of other risk factors for macrovascular disease, including hyperglycemia, increases the susceptibility to atherosclerotic disease. Various causal mechanisms for a linkage between insulin resistance and macrovascular complications have been proposed.

It has been suggested that insulin resistance in pathways other than glucose metabolism may increase the risk of atherosclerosis. For example, actions of insulin on endothelial cells, such as stimulating the generation of the local vasodilator nitric oxide, have been demonstrated and this potentially beneficial effect of insulin appears to be blunted in insulin-resistant subjects with obesity and/or type 2 diabetes. Such a form of insulin resistance, expressed as subnormal generation of nitric oxide, could promote cardiovascular events by diminishing the normal inhibitory actions of nitric oxide on vascular smooth muscle cell proliferation, platelet adhesive-

ness, vasoconstriction, or the development of hypertension.

Hyperinsulinemia is an almost invariable compensatory accompaniment to insulin resistance, and has received particular attention as one crucial atherogenic or thrombogenic agent. Elevated insulin levels required to compensate for resistance to insulin-stimulated glucose metabolism or disposition might still be normally (or even supernormally) active in other pathways of insulin action, such as its effects on mitogenesis. Evidence has been advanced, although controversial, for a hypothesis that hyperinsulinemia secondary to insulin resistance might sensitize cells, such as vascular smooth muscle cells or endothelial cells, to the mitogenic effects of various growth factors. However, epidemiological evidence that hyperinsulinemia itself, independent of diabetes, and other macrovascular disease risk factors, is a strong risk factor for macrovascular complications is conflicting. Data from some recent studies have questioned this hypothesis.

In some, but not all populations, hypertension and insulin resistance coexist, but correlation between blood pressure and plasma insulin levels is inconsistent and relatively weak. Furthermore, as noted above, administered insulin has a direct vasodilating not a vasoconstricting effect, and blood pressure is not elevated in hyperinsulinemic patients with insulinoma or in type 1 diabetic subjects prior to developing nephropathy, or without a family history of essential hypertension.

Hyperinsulinemia or insulin resistance could increase the risk of atherosclerotic disease by aggravating the dyslipidemia with which it is associated. For example, insulin has the ability to increase VLDL (triglyceride) output by the liver. However, exogenous insulin treatment of type 2 diabetes lowers serum triglyceride levels as it lowers glucose levels. HDL cholesterol levels tend to increase, and LDL cholesterol levels change inconsistently. Importantly, intervention studies have shown a marked reduction in cardiovascular events in diabetic individuals whose LDL levels were decreased by an HMG-CoA reductase inhibitor. More complex mechanistic interrelationships among insulin resistance, abdominal adiposity, and dyslipidemia have been proposed that are under investigation.

Finally, specifically treating insulin resistance per se, as opposed to treating the other atherosclerotic risk factors with which it is associated, has not yet been shown to reduce the incidence of cardiovascular, cerebrovascular, or peripheral vascular complications. This possibility is being tested in the current DPP (described above), in which these complications or their surrogates are being studied as secondary outcomes. In the meantime, elimination of those components of the insulin resistance syndrome that are individually amenable to treatment remains the top priority in management of diabetes. Hyperglycemia, hypertension, dyslipidemia, obesity, and a sedentary existence must be aggressively attacked along with other major risk factors such as smoking.

APPENDIX

Consensus panel

Saul Genuth, MD, Chair; Michael A. Brownlee, MD; Lewis H. Kuller, MD; Ellis Samols, MD; Christopher D. Saudek, MD; and Robert Sherwin, MD.

Presenters at the conference

Alain D. Baron, MD; Richard N. Bergman, PhD; Guenther H. Boden, MD; Clifton Bogardus, MD; John D. Brunzell, MD; Barbara E. Corkey, PhD; Boris Draznin, MD, PhD; Andrea Dunaif, MD; Diane T. Finegood, PhD; Henry N. Ginsberg, MD; Barbara V. Howard, PhD; Markku Laakso, MD; Braxton Mitchell, MPH, PhD; Jerrold M. Olefsky, MD; Daniel Porte, Jr., MD; Robert A. Rizza, MD; Luciano Rossetti, MD; Mohammed F. Saad, MD, MRCP; and Robert S. Schwartz, MD.

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