Reduced Early Insulin Secretion in the Etiology of Type 2 Diabetes Mellitus in Pima Indians

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We report the results of cross-sectional, prospective, and longitudinal studies identifying etiologic metabolic factors in the susceptibility to type 2 diabetes mellitus of the Pima Indians of Arizona, whose prevalence and incidence rates of the disease are the highest in the world. Diabetic Pima Indians are metabolically prototypic, with obesity, insulin resistance, a reduced acute insulin response to glucose, and increased endogenous glucose production. Cross-sectional studies show that the acute insulin response is absent in diabetic subjects and lower in impaired than in normal glucose-tolerant subjects. Prospective studies using proportional hazards analyses indicate that insulin resistance and a relatively low acute insulin response predict diabetes independently of age, gender, and each other, with obesity increasing susceptibility by worsening one or both predictors. Longitudinal studies show that glucose tolerance deteriorates as the degree of obesity increases due to worsening insulin resistance and decreases in early insulin secretion. Furthermore, since the children of diabetic pregnancies are at much greater risk of developing diabetes at a young age than those of nondiabetic pregnancies, the diabetic uterine environment may induce insulin resistance and/or reduced insulin secretion: early evidence confirms that adult normal glucose-tolerant offspring show a substantially decreased acute insulin response—the clearest demonstration yet of an environmental condition increasing susceptibility to type 2 diabetes mellitus. However, the genetic determinants require elucidation: correlation of the acute insulin response with the age of parental diabetes onset in fathers as well as mothers indicates a mechanism independent of the diabetic uterine environment. Diabetes 51 (Suppl. 1):S262–S264, 2002

The Pima Indians of Arizona, U.S., have the highest reported prevalence and incidence rates of type 2 diabetes mellitus in the world. With the Pimas’ cooperation, cross-sectional, prospective, and longitudinal studies have been conducted to identify the etiologic metabolic factors that increase susceptibility to this disease. The results of several early studies indicated that the Pimas, on average, are more insulin resistant than whites, and this contributes to their higher prevalence of diabetes. More recent studies have proven that, in addition to insulin resistance, a relatively lower acute insulin secretory response to glucose is also a major etiologic determinant of diabetes susceptibility in this population. A reduced acute insulin response (AIR) appears to result from both environmental and genetic factors. Cross-sectional studies. Pima Indians who were not known to have diabetes mellitus were admitted to the clinical research ward for 10–14 days. After informed consent, and as described in detail previously (1), these volunteers underwent studies of 1) body composition by underwater weighing or dual X-ray absorptiometry; 2) oral glucose tolerance test; 3) measures of the AIR to a 25-g intravenous bolus injection of glucose (AIR was calculated as the mean plasma insulin concentration 3, 4, and 5 min after the injection); 4) measures of the rate of postabsorptive production of endogenous glucose using tritiated glucose; and 5) measures of insulin action in vivo using a two-step, hyperinsulinemic, euglycemic clamp. These studies were approved by the Institutional Review Board of the National Institutes of Diabetes and Digestive and Kidney Diseases and by the Tribal Council of the Gila River Indian Community.

The metabolic characteristics of Pima Indians with type 2 diabetes are prototypic of the disease worldwide. The disease is characterized by obesity, insulin resistance, a reduced AIR to glucose, and an increased rate of endogenous glucose production (2). The insulin resistance is not entirely a result of obesity (3).

In nondiabetic individuals, the degree of glycemia is positively correlated with plasma insulin concentrations and negatively with insulin action (4). In people with diabetes, the degree of glycemia is negatively correlated with plasma insulin concentrations (4). Although all those with diabetes are insulin resistant, there is no correlation between degree of glycemia and insulin action (4). The rate of endogenous glucose production is not correlated with glycemia in nondiabetic individuals, but is closely
and a relatively low AIR were also predictive (both independent of age, sex, and degree of obesity; insulin resistance and/or increased slightly in those who remained normal glucose tolerant over the same 5-year period also were analyzed.

Mean body weight increased by ~13 kg in the prediabetic group and by ~6 kg in the control group. Commensurate with the increased degree of obesity, insulin action decreased in both groups. However, changes in AIR were strikingly different in the two groups. AIR decreased in the transition from normal to impaired glucose tolerance in the prediabetic group and declined further with the development of diabetes. In contrast, AIR remained unchanged or increased slightly in those who remained normal glucose tolerant (Fig. 2).

The rate of basal endogenous glucose production remained unchanged in the control group over the period of follow-up. In the prediabetic group, the rate of basal endogenous glucose production did not change during the transition from normal to impaired glucose tolerance and increased slightly with the development of diabetes (5).

Conclusions from cross-sectional, prospective, and longitudinal studies. Type 2 diabetes mellitus in Pima Indians is characterized by obesity, insulin resistance, positively correlated with glycemia in those with diabetes (4).

In addition, the AIR is generally absent in people with diabetes (2). In nondiabetic subjects, the mean AIR of those with impaired glucose tolerance is lower than the mean AIR of those with normal glucose tolerance (2).

The results of these cross-sectional studies indicate clearly that Pima Indians with diabetes are insulin resistant. However, the degree of glycemia in this group is dependent on the abnormally elevated rate of endogenous glucose production and the extent of reduction in plasma insulin concentrations.

The abnormal insulin secretory function is also evident from the absence of AIR to glucose. However, from these cross-sectional studies, it cannot be determined which of these metabolic characteristics is etiologic or which is a secondary abnormality resulting from the disease process. This can only be determined from prospective studies.

Prospective studies. A prospective study was undertaken to identify which of the metabolic abnormalities characteristic of people with diabetes were predictive of the development of diabetes in Pima Indians with normal glucose tolerance. This was done by asking individuals to return yearly to the clinical research ward to repeat the metabolic studies.

After a mean duration of follow-up of about 7 years, 48 of 300 individuals who initially had normal glucose tolerance developed diabetes. Proportional hazards analyses indicated that independent of age and sex, degree of obesity was a predictor of diabetes (P < 0.01). Independent of age, sex, and degree of obesity, insulin resistance and a relatively low AIR were also predictive (both P < 0.01) (Fig. 1).

These results indicate that, as originally hypothesized, the most insulin-resistant Pimas were at increased risk of diabetes. Somewhat surprisingly, a low AIR was equally predictive of the disease. The rate of endogenous glucose production was not predictive and therefore appears to be a metabolic abnormality that occurs secondary to the disease process. Furthermore, obesity was not predictive independently of AIR and insulin action, indicating that obesity increases susceptibility to diabetes by worsening insulin action and/or worsening AIR.

Thus, three of the four major metabolic characteristics of people with diabetes—obesity, insulin resistance, and a low AIR—are present (to a lesser extent) in prediabetic subjects, even when they have normal glucose tolerance.

Longitudinal studies. To delineate the natural history of the metabolic deterioration from normal to impaired glucose tolerance and to diabetes, analyses were performed on repeated measurements of body composition, insulin action, and insulin secretory function made on 17 Pimas who developed diabetes (5). Data from a control group of 31 individuals who remained normal glucose tolerant over the same 5-year period also were analyzed.

Mean body weight increased by ~13 kg in the prediabetic group and by ~6 kg in the control group. Commensurate with the increased degree of obesity, insulin action decreased in both groups. However, changes in AIR were strikingly different in the two groups. AIR decreased in the transition from normal to impaired glucose tolerance in the prediabetic group and declined further with the development of diabetes. In contrast, AIR remained unchanged or increased slightly in those who remained normal glucose tolerant (Fig. 2).

The rate of basal endogenous glucose production remained unchanged in the control group over the period of follow-up. In the prediabetic group, the rate of basal endogenous glucose production did not change during the transition from normal to impaired glucose tolerance and increased slightly with the development of diabetes (5).

Conclusions from cross-sectional, prospective, and longitudinal studies. Type 2 diabetes mellitus in Pima Indians is characterized by obesity, insulin resistance, independently of AIR and insulin action, indicating that obesity increases susceptibility to diabetes by worsening insulin action and/or worsening AIR.

Thus, three of the four major metabolic characteristics of people with diabetes—obesity, insulin resistance, and a low AIR—are present (to a lesser extent) in prediabetic subjects, even when they have normal glucose tolerance.
reduced early insulin secretion, and increased rates of endogenous glucose production. Of these four metabolic abnormalities, the first three are already present in prediabetic subjects with normal glucose tolerance. The rate of endogenous glucose production increases later in the natural history of the disease. Glucose tolerance deteriorates as the degree of obesity increases due to worsening insulin resistance and decreases in early insulin secretion, which is often absent with the onset of diabetes.

Environmental and genetic determinants of early insulin secretion. Since a relatively low AIR is a major risk factor for diabetes in the Pimas, studies were conducted to identify determinants of AIR in Pimas with normal glucose tolerance. It was previously established that the offspring of diabetic pregnancies were at much greater risk of developing diabetes at a young age compared with the offspring of nondiabetic pregnancies (6). It was hypothesized, therefore, that the diabetic uterine environment resulted in insulin resistance and/or reduced insulin secretion. Studies indicate that the adult, normal glucose-tolerant offspring are no more insulin resistant than the control group, but have substantially reduced AIRs to glucose (8). This is the clearest demonstration of an environmental condition that increases susceptibility to type 2 diabetes mellitus. Studies are currently underway to more fully characterize the insulin secretory function of the offspring of diabetic pregnancies by measuring insulin responses to graded glucose infusions resulting in a broad range of plasma glucose concentrations.

Data have also been obtained to indicate that there are genetic determinants of AIR in normal glucose-tolerant Pima Indians. AIR is a highly heritable trait, independent of degree of obesity and insulin action (7). In addition, independent of obesity and insulin action, our data indicate that AIR is correlated with the age of onset of diabetes in the parents (8). This correlation appears to be evident for both the age of onset of diabetes in fathers as well as mothers and therefore is not the result of the effects of a diabetic uterine environment. The most plausible explanation for these observations is that the earlier age of onset of diabetes in the parents results from lower AIRs (which is consistent with the prospective data that a lower AIR is a risk factor for diabetes) and that AIR has genetic determinants that are expressed in the offspring.

CONCLUSIONS
A relatively lower AIR is a major risk factor for diabetes in Pima Indians, independent of obesity and insulin resistance. The diabetic intrauterine environment appears to be associated with a lower AIR in the offspring. AIR also apparently has major genetic determinants based on its heritability and correlation with age of onset of parental diabetes.

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REFERENCES