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Pathogenesis of NIDDM in Pima Indians

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Abstract
The Pima Indians of Arizona have the highest reported prevalence and incidence of non-insulin-dependent diabetes mellitus (NIDDM) of any population in the world. A cross-sectional and longitudinal study was begun in 1982 to determine the metabolic characteristic(s) that is (are) predictive of the development of NIDDM and to document the sequence of metabolic events that occur with the transition from normal to impaired glucose tolerance and then to diabetes. Preliminary analyses suggest that insulin resistance is a primary abnormality predisposing Pima Indians to develop impaired glucose tolerance, and that the development of diabetes occurs with subsequent pancreatic failure.

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Pathogenesis of NIDDM in Pima Indians

The Pima Indians of Arizona have the highest reported prevalence and incidence of non-insulin-dependent diabetes mellitus (NIDDM) of any population in the world. A cross-sectional and longitudinal study was begun in 1982 to determine the metabolic characteristic(s) that is (are) predictive of the development of NIDDM and to document the sequence of metabolic events that occur with the transition from normal to impaired glucose tolerance and then to diabetes. Preliminary analyses suggest that insulin resistance is a primary abnormality predisposing Pima Indians to develop impaired glucose tolerance, and that the development of diabetes occurs with subsequent pancreatic failure. *Diabetes Care* 14 (Suppl. 3):685–90, 1991

The Pima Indians are a relatively genetically homogenous population who have lived in the same hot, arid environment in Arizona for nearly 2000 years (1). They were traditionally an agricultural society, making use of the Gila River and an extensive system of irrigation canals to supply enough water to grow sufficient produce to survive in this hostile environment. In the latter part of the last century, and in the early part of this century, the Gila River began to dry up as a result of increased water use by upstream settlers and ultimately with the damming of the river. The Pima Indians were catapulted from a self-sufficient agrarian society to a "westernized" society that depended on purchased (or government-issued) foods for their survival. With the abrupt radical change in lifestyle has come obesity (2), and with the obesity has come the highest reported prevalence and incidence of non-insulin-dependent diabetes mellitus (NIDDM) of any population in the world (3).

Since the mid-1960s the residents of the Gila River Indian Community have willingly participated in a longitudinal study of the development of NIDDM. Every 2 yr, members of the community >5 yr of age are examined in the clinic of the National Institute of Diabetes and Digestive and Kidney Diseases. Many important observations regarding risk factors for the development of NIDDM in the population have been identified in this collaborative epidemiological effort. Some of the risk factors identified among nondiabetic subjects have included age, glucose intolerance, body mass index, and parental diabetes (2).

Approximately 6 yr ago an in-depth longitudinal study of a subset of the Pima population was begun with the purposes of 1) defining the metabolic characteristic(s) that is (are) predictive of the development of NIDDM and 2) documenting the sequence of metabolic events that occurs with the transition from normal to impaired glucose tolerance and then to NIDDM. We report herein preliminary analyses of the data collected in the cross-sectional and early longitudinal phases of this study.

### CROSS-SECTIONAL STUDIES

People with fasting glycemia >13.8 mM and NIDDM are most often characterized by obesity, relatively low plasma insulin concentrations, insulin resistance, and increased rates of hepatic glucose production. In our
initial cross-sectional studies, we determined the relationship between these metabolic abnormalities and fasting glycaemia among nondiabetic subjects and untreated diabetic patients.

The hyperinsulinaemic-euglycaemic clamp technique was used to estimate insulin action in vivo at both physiological (~600 pM) and maximally stimulating insulin concentrations (~12,000 pM; Figs. 1 and 2). At both insulin levels, people with NIDDM were uniformly insulin resistant, i.e., they had very low rates of insulin-mediated glucose disposal (4). However, there was no significant correlation between fasting glycaemia and insulin action at either insulin level. Conversely, among the nondiabetic subjects, there was a wide range of insulin action, and the degree of insulin resistance was proportional to the level of glycaemia at both low and maximally stimulating insulin concentrations.

Two important tentative conclusions can be drawn from these data. First, although insulin resistance is uniformly present among those with NIDDM, it appears that people with fasting glycaemia of ~16.6 mM are no more resistant than those diabetic subjects with fasting glycaemia of ~8.3 mM. Therefore, an additional metabolic abnormality must occur to result in changes in fasting glycaemia in this range. Second, because insulin action was significantly negatively correlated with glycaemia among nondiabetic subjects, insulin resistance could be the mechanism of their impaired glucose tolerance in this group.

Studies of the insulin levels in these same subjects are consistent with these measurements of insulin action. Among diabetic subjects, there was a significant negative correlation between glycemia and fasting plasma insulin concentration (Fig. 3). Similar relationships were observed between the insulin response to an oral glucose load or to a mixed meal (4). Among nondiabetic subjects, those with the worst glucose tolerance had the highest insulin levels; the insulin levels were as expected for their level of glycaemia, with the use of subjects with normal glucose tolerance as a reference (5). These data further supported the hypothesis that insulin resistance was a major cause of impaired glucose tolerance among nondiabetic subjects, but among diabetic subjects impaired insulin secretion (and/or increased insulin clearance) also occurred to contribute to the pathogenesis of increasing glycaemia.

In addition, among diabetic subjects, a strong correlation was observed between fasting glycaemia and the rate of hepatic glucose production, as estimated with tracer methodology and tritiated glucose (4; Fig. 4). There was no correlation between glycaemia and hepatic glucose production rate among nondiabetic subjects (4). Among diabetic subjects, there were also significant linear correlations between fasting glycaemia, free fatty acid levels, and rates of hepatic glucose production (4). Free fatty acids may contribute to the stimulation of increased hepatic glucose production by two mechanisms (6–8). First, free fatty acid oxidation can provide the energy needed for increased gluconeogenesis. Second, an increased influx of free fatty acids into a limb results in an increased efflux of lactate, presumably by the inhibition of pyruvate dehydrogenase (9). The increased lactate efflux from the limb to the liver can then provide a ready supply of three-carbon substrates for gluconeogenesis.

These cross-sectional data suggest the following hypothesis of the pathogenesis of NIDDM among Pima Indians. Among nondiabetic subjects, impaired glucose tolerance is a result of insulin resistance. The pancreas
C. BOGARDUS, S. ULLIOJA, AND P.H. BENNETT

FIG. 3. Relationship between fasting plasma insulin and glucose concentrations. ●, Diabetic subjects ($r = 0.69$, $P < 0.01$); ○, nondiabetic subjects ($r = 0.24$, NS).

responds appropriately with increased insulin secretion, resulting in the commonly observed hyperinsulinemia among these subjects. More severe hyperglycemia results from the additional metabolic defect of failing pancreatic function and declining plasma insulin levels. By indirect and possibly through direct effects, declining plasma insulin levels result in increased hepatic glucose production in subjects with preexisting insulin resistance.

Inherent in these hypotheses is a primary role for insulin resistance in the pathogenesis of NIDDM in this population. Because NIDDM has significant and major genetic determinants (10), the hypotheses would be strengthened by evidence of genetic determinants of insulin resistance, particularly among nondiabetic subjects, i.e., before NIDDM develops. With this in mind, we have analyzed the determinants of insulin resistance among Pima Indians.

Obesity is commonly believed to be a major determinant of insulin resistance in humans. Therefore, the relationship between degree of obesity, as estimated by densitometry, and insulin action in vivo was determined in a large number of nondiabetic Pima Indians at both physiological and maximally stimulating insulin concentrations (11–13; Figs. 5 and 6).

At physiological insulin concentrations, degree of obesity was nonlinearly correlated with insulin action (Fig. 5). However, above a body fat of 30% there was no significant correlation between these two parameters. Also, at any given degree of obesity there was considerable variance in insulin action, suggesting the importance of determinants of insulin action not related to degree of obesity. At maximally stimulating insulin concentrations, insulin action and degree of obesity were linearly but more weakly correlated, i.e., obesity accounted for even less of the variance in insulin action. Thus, although there is evidence that the obese are more insulin resistant, the impact of obesity on insulin action is probably less than previously thought.

Multivariate analyses showed that, at physiological insulin concentrations, obesity accounted for ~36% of the variance in insulin action in vivo, and at maximally

FIG. 4. Relationship between endogenous (hepatic) glucose production rate and fasting plasma glucose concentration. Endogenous glucose production rate was measured with [3-3H]glucose as tracer in the morning after an overnight fast. ●, Diabetic subjects ($r = 0.90$, $P < 0.001$); ○, nondiabetic subjects ($r = 0.33$, NS).

FIG. 5. Relationship between insulin-mediated glucose disposal rate and percentage body fat. Glucose disposal rate was measured during a hyperinsulinemic (mean ± SE plasma insulin concentration 756 ± 18 pM) euglycemic (mean plasma glucose concentration 5.2 ± 0 mM) clamp. Percentage body fat was estimated by densitometry ($n = 213$, $r = -0.61$, $P < 0.0001$). EMBS, estimated metabolic body size.
DIABETES MELLITUS IN PIMA INDIANS

FIG. 6. Relationship between maximal insulin-mediated glucose disposal rate and percentage body fat. Glucose disposal rate was measured during a hyperinsulinemic (mean ± SE plasma insulin 11,886 ± 210 pM) euglycemic (mean ± SE plasma glucose concentration 5.2 ± 0.06 mM) clamp. Percentage body fat was determined by densitometry (n = 213, r = −0.30, P < 0.0001). EMBS, estimated metabolic body size.

stimulating insulin concentrations accounted for only ~15% of the variance in insulin action (13). In addition, age and sex differences did not account for much of the variance in insulin action not accounted for by obesity (13). The differential impact of obesity on insulin action at physiological versus maximally stimulating insulin concentrations is not fully explained. However, as we have previously suggested, it may relate to the reduced skeletal muscle capillary density that occurs with obesity (14).

What emerged from these analyses, however, was that insulin action, independent of the effect of obesity, age, and sex, aggregates in families (13; Fig. 7). This familial aggregation was consistent with either significant genetic factors and/or family-based environmental factors being significant determinants of insulin action in vivo among Pima Indians. Because the subjects were studied after living on our metabolic ward for ~1 wk, and because they were adults who frequently did not share the same home environment, the data are most consistent with a hypothetical role for genetic factors in determining insulin action in this population.

To summarize the cross-sectional results, it appeared that, among nondiabetic subjects, insulin resistance is a major determinant of impaired glucose tolerance and that the insulin resistance is probably a result of both genetic and so-called “environmental factors” such as degree of obesity. More severe hyperglycemia results from the pancreatic failure superimposed on insulin resistance.

LONGITUDINAL STUDIES

These hypotheses of the pathogenesis of NIDDM among Pima Indians were based on cross-sectional data and may not accurately reflect the longitudinal sequence of events. Only prospective longitudinal studies have the potential to unequivocally determine the pathogenetic mechanisms of the development of NIDDM. Our longitudinal studies are still ongoing but some preliminary observations can be reported.

The cross-sectional data suggested that impaired glucose tolerance was largely a result of insulin resistance rather than being a result of any deficit in insulin secre-

FIG. 7. Maximal insulin-stimulated glucose disposal rate (MaxM) adjusted for age, sex, and percentage body fat is shown for each subject (*). Subjects are grouped by family (bars) and families are ranked by family mean adjusted MaxM (−). Family effect on MaxM was significantly independent of percentage body fat, age, and sex (P < 0.0001). EMBS, estimated metabolic body size.

FIG. 8. Longitudinal changes in subjects with normal glucose tolerance in whom glucose tolerance became impaired over 21.5 mo of follow-up (range 10–45 mo). Individual values and means (bars) are shown for insulin area during an oral glucose tolerance test (OGTT) and glucose uptake during hyperinsulinemia (~780 pM) and euglycemia (~5.5 mM).
C. BOGARDUS, S. LILLIOJA, AND P.H. BENNETT

FIG. 9. Insulin and glucose areas derived from oral glucose tolerance tests (OGTTs) on 278 Pima Indians. Shown are means (with 95% confidence limits) for each of 4 study groups: subjects with normal glucose tolerance \((n = 151)\), subjects with impaired glucose tolerance (IGT; \(n = 90\)), subjects with fasting plasma (FG) glucose values \(<6.6\) mM \((n = 11)\), and subjects with FG levels \(>6.6\) mM \((n = 26)\). Regression lines are shown for nondiabetic and diabetic subjects. Arrow, mean value for subjects before and after development of IGT \((n = 24)\).

Some of these subjects, who made the transition from normal to impaired glucose tolerance did develop NIDDM during follow-up. In addition, some people who had impaired glucose tolerance at entry into the study have developed NIDDM during follow-up. As reported previously, among 145 nondiabetic subjects studied and followed for an average of 1.8 yr, 18 people developed NIDDM (15). At entry into the study, these subjects were more hyperinsulinemic and insulin resistant than the nondiabetic subjects who did not develop NIDDM. This was the first suggestion, although still preliminary, that insulin resistance is a predictor of the development of NIDDM among nondiabetic Pima Indians. Whether these data will hold up with a longer duration of follow-up remains to be seen. Nonetheless, our preliminary longitudinal data appear to corroborate tentative conclusions drawn on the basis of the cross-sectional analyses.

Insulin resistance appears to be a primary abnormality that predisposes Pima Indians to develop NIDDM at an increased rate. Insulin resistance leads to an impaired glucose tolerance and this is followed by pancreatic failure that is then associated with marked fasting hyperglycemia. Whether the pancreatic failure is a consequence of insulin resistance (i.e., β-cell exhaustion or glucotoxicity) or a result of other predetermined genetic factors is uncertain. A more thorough understanding of all of these events will be forthcoming when sufficient numbers of people have been observed to proceed through the proposed sequence of metabolic events in the transition from normal glucose tolerance to NIDDM.

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