Reduced Insulin Secretion in Offspring of African Type 2 Diabetic Parents

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OBJECTIVE — To determine the early biochemical predictors of increased susceptibility to develop diabetes in offspring of African type 2 diabetic parents.

RESEARCH DESIGN AND METHODS — A total of 69 offspring (case subjects) of 26 families in Cameroon with at least one type 2 diabetic parent were studied, and 62 offspring (control subjects) from 29 families in Cameroon with no parent with type 2 diabetes underwent an oral glucose tolerance test. Early insulin secretion was calculated using the ratio of the 0- to 30-min incremental insulin values to the 0- to 30-min incremental glucose. Anthropometric parameters were also measured.

RESULTS — Of the case subjects, 23% were glucose intolerant (4% with diabetes and 19% with impaired glucose tolerance [IGT]) compared with 6.5% (all with IGT) of control subjects (P = 0.02). There was also an increasing prevalence of glucose intolerance, especially IGT with increasing number of glucose-intolerant parents. Fasting serum insulin levels were not different in the two groups; however, at 30 min, the case subjects had lower insulin levels than the control subjects (P < 0.006). Case subjects with IGT had lower 30-min insulin concentration, early insulin secretion, and 2-h insulin levels than those with normal glucose tolerance (NGT) (F = 4.1, P < 0.05; F = 4.1, P < 0.04; and F = 5.1, P < 0.03, respectively). Furthermore, case subjects with NGT and IGT had lower early insulin secretion than control subjects (F = 4.1, P < 0.03). These differences remained after adjustment for BMI and regardless of the status of parental diabetes. Two-hour insulin concentration showed a positive association (odds ratio = 0.93 CI 0.90–0.99, P = 0.039) with IGT in the case subjects.

CONCLUSIONS — Diabetes and IGT are more prevalent in the offspring of African type 2 diabetic parents, and this may be due to an underlying degree of β-cell impairment marked by reduced early-phase insulin secretion.

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Type 2 diabetes is known to result from the interaction of genetic and environmental factors (1). Although genetic susceptibility is probably a prerequisite, other factors, including degree of obesity; decreased physical activity; poor dietary habits with excessive consumption of fat, sugar, and refined carbohydrates; and increasing age, influence the development of type 2 diabetes (1).

The role of heredity is demonstrated by the fact that a strong familial aggregation is characteristic of type 2 diabetes (2), and studies of identical twins show a concordance rate that approaches 100% with age (1,3–5). Therefore, the predisposition to develop this disease is strongly determined by genetic factors. Indeed, in some populations, the offspring of type 2 diabetic parents are at greater risk of developing the disease than offspring of unaffected parents (1,6–8). Information about whether the offspring of type 2 diabetic parents are at greater risk of developing the disease than offspring of nondiabetic parents is not available in African type 2 diabetic patients.

Although type 2 diabetes is not clinically apparent until adulthood, metabolic abnormalities may be present and detectable much earlier. This suggests that even in apparently unaffected offspring of type 2 diabetic parents, insulin secretion and insulin metabolic abnormalities may be present, and glucose intolerance may be found long before the onset of type 2 diabetes (9).

Data on the pathogenesis of type 2 diabetes in black Africans are scarce, and its pathogenesis is poorly understood. This study was undertaken to determine the early biochemical predictors of increased susceptibility to develop diabetes in offspring of African type 2 diabetic parents.

RESEARCH DESIGN AND METHODS — Nuclear pedigrees of known type 2 diabetic patients attending the diabetes clinic were selected by consecutive sampling. Participants were offspring of type 2 diabetic patients. Patients had diabetes diagnosed after the age of 30 years with no history of ketosis and had been treated initially with diet alone or diet and oral hypoglycemic agents. Only type 2 diabetic patients whose spouses were alive and available for testing, with at least two-thirds of their offspring living in Yaoundé, aged 20 years and older and available for testing, were included in the study.

The control population was selected on the basis of the tribal and socioeconomic status of the diabetic population from the Cité Vert Yaoundé community registry (10). It consisted of offspring of parents without type 2 diabetes matched for age-group and sex to the offspring of type 2 diabetic parents. The parents without diabetes all had normal glucose tolerance (NGT) tests and no family history of diabetes. A total of 69 offspring of 26 families in Cameroon with at least one parent with type 2 diabetes were...
studied, and 62 offspring from 25 families in Cameroon with no parent with type 2 diabetes served as control subjects. After informed consent was obtained from the subjects, they were invited to the Diabetes Research Laboratory of the University Hospital Centre at 7:00 A.M. after an overnight fast. The Ethics Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé 1 approved the study protocol.

An oral glucose tolerance test (OGTT) was performed according to the World Health Organization protocol (11). Glucose was ingested in 300 ml water corresponding to 75 g anhydrous glucose between 7:00 and 10:00 A.M. after an overnight fast of at least 12 h. In every subject, 12.5 ml whole blood was drawn from an antecubital vein into appropriate tubes 0, 15, 30, 60, and 120 min after the glucose load for the determination of plasma glucose, insulin, C-peptide, cholesterol, and triglycerides. Blood for insulin and C-peptide determinations was collected on ice, centrifuged immediately, separated, and stored at −70°C until assayed. Each subject also completed a lifestyle questionnaire and had anthropometric measurements and blood pressure taken. Height and weight were measured once, with subjects dressed in light clothing and without shoes. Weight was measured to the nearest 0.1 kg using a regularly calibrated digital electronic scale. Height was measured using a stadiometer with the head held in the Frankfurt plane and the subject standing erect without shoes. BMI was calculated as weight/height². Waist and hip circumferences were measured as previously described (10) with subjects standing erect and their abdomen relaxed, arms hanging down at the sides of their body, and their heels together. The mean of the three measurements was recorded for the calculation of the waist-to-hip ratio.

Participants were seated for 30 min before diastolic and systolic blood pressures were recorded three times on the right arm using a standard mercury sphygmomanometer with a cuff bladder measuring 23 × 12 cm or larger for obese individuals. Systolic and diastolic blood pressures were defined as the first- and fifth-phase Korotkoff sounds, respectively. The average of the second and third recordings was used in the present analyses.

Plasma glucose was measured on site by the glucose oxidase method (HemoCue B-glucose Spectrophotometer; HemoCue, Angelholm, Sweden) and confirmed by a Cobas bio hexokinase fluorometric method. The linear correlation coefficient between the two methods was 0.96, with a mean difference of 0.17 mmol/l, which did not increase with increasing glucose levels, and the laboratory coefficient of variation was as follows: low, 6.3%; medium, 3.1%; and high, 2.5% for the C-peptide assay, and for the insulin assay: low, 8.7%; medium, 2.7%; and high, 2.6%. Serum cholesterol and triglycerides were measured by enzymatic methods. Early insulin secretion was calculated using the ratio of the 0- to 30-min incremental insulin values to the 0- to 30-min incremental glucose (4,14).

Statistical analysis

Data were entered in a personal computer using the Statistical Package for Social Science for Windows. Results were expressed as means ± SD except where otherwise stated. Comparison between groups was done using the analysis of variance F test. Logarithms of glucose, insulin, and C-peptide concentrations were used in the statistical analyses to normalize the distributions. The χ² test with continuity correction was used where necessary. Multivariate logistic regression was used to estimate the odds ratios (ORs) for IGT and diabetes according to the various parameters, comparing the upper quartile and the median after adjusting for age, and age and BMI. P values <0.05 were taken to indicate statistical significance. Data from the OGTT were used to calculate the ratio of the 0- to 30-min increment in insulin to the 0- to 30-min increment in plasma glucose (14,15). The areas under the curves were calculated using a previously published formula (16).

RESULTS — The mean age at diagnosis of diabetes in parents was 51.8 ± 8.5 and 50.3 ± 8.9 years, respectively, for fathers and mothers with type 2 diabetes. The mean known duration of diabetes was 11.11 ± 7.06 years in the fathers and 7.00 ± 6.36 years in the mothers. Of the 26 families, there were 4 families in which both parents had diabetes, 2 families in which one parent had type 2 diabetes and the other had IGT, and 20 families in which only 1 parent had type 2 diabetes. A total of 69 offspring, representing 90% of all the offspring of 26 families with at least one parent with type 2 diabetes (case subjects), compared with 62 offspring, representing 90% of all the offspring of 25 families with no parent with type 2 diabetes (control subjects), were studied. The two groups were similar in age, BMI, and waist-to-hip ratio, but the case subjects had higher fasting and 2-h plasma glucose levels (P < 0.001) than the control subjects (Table 1).
Of the case subjects, 23% were glucose intolerant (4% with diabetes and 19% with IGT) compared with 6.5% (all with IGT) of control subjects \((P = 0.02)\). There was also an increasing prevalence of glucose intolerance, especially IGT with increasing number of glucose-intolerant parents. Of the 51 offspring from the 20 families with one diabetic parent, 43 (84%), 5 (10%), and 3 (6%), respectively, had NGT, IGT, and type 2 diabetes. Five offspring (62.5%) had NGT and three (37.5%) had IGT when one parent was diabetic and another had IGT; five (50%) each had NGT and IGT when both parents had type 2 diabetes. In the control group, 58 (93%) had NGT and 4 (6.5%) had IGT. Thus, there was respectively 16 and 44% glucose intolerance among the offspring when one or both parents were glucose intolerant. The sex of the glucose-intolerant parent did not seem to affect the glucose tolerance status of the offspring \((P = 0.4)\). Some 50% of those with IGT in the control population were obese \((\text{BMI} \geq 30 \text{ kg/m}^2)\) compared with 8% of the case subjects.

The glucose, insulin, and C-peptide responses to the 75-g glucose load are shown in Fig. 1. The case subjects had significantly higher mean plasma glucose levels throughout the OGTT than the control subjects; the area under the glucose response curves was 516 versus 434 \((F = 30.3, P < 0.001)\). Fasting serum insulin and C-peptide levels were not different in the two groups; however, at 30 min, the case subjects had a lower insulin level than the control subjects \((P < 0.006)\). Also, the C-peptide levels were significantly lower in case subjects than in the control subjects both at 15 and 30 min \((P < 0.003)\). The insulin–to–C-peptide ratio was similar in both groups. These differences remained after adjustment for BMI and regardless of the status of parental diabetes. The areas under the insulin response curves were significantly lower in case subjects than in the control subjects \((2,329 \text{ vs. } 3,233; F = 5.6, P = 0.02)\) (Fig. 1).

Table 2 compares the case subjects and control subjects with NGT and those with IGT. Fasting plasma glucose levels were different in all of the groups. The case subjects with IGT had lower 30-min insulin secretion, early insulin secretion, and 2-h insulin levels than those with NGT \((F = 4.1, P < 0.05; F = 4.1, P < 0.04; \text{and } F = 5.1, P < 0.03, \text{respectively})\). The control subjects with NGT and IGT had similar levels. However, case subjects with NGT and IGT had lower early insulin secretion than control subjects \((F = 4.1, P < 0.03)\). Also, early insulin secretion was lower \((P < 0.02)\) in case subjects than in control subjects with NGT. These differences remained after adjustment for BMI and regardless of the status of parental diabetes.

Multiple logistic regression analysis showed that the area of insulin response had a positive association \((\text{ORs} = 0.93 \text{ CI } 0.89–0.97, P = 0.037)\) and early insulin secretion had a negative association \((\text{OR} = -0.96 \text{ CI } 0.93–0.99, P = 0.022)\) with IGT in the case subjects but not in the control subjects; these associations were observed even after adjusting for age and BMI. Age, sex, BMI, waist-to-hip ratio, fasting and 2-h insulin, area under the insulin curve, and the C-peptide measurements did not show independent associations in both groups. Two-hour insulin showed a positive association \((\text{OR} = 0.95 \text{ CI } 0.90–0.99, P = 0.039)\) with IGT in the case subjects.

**CONCLUSIONS** — Our results indicate that the offspring of African type 2 diabetic parents show a higher prevalence of glucose intolerance than offspring of parents without diabetes, and this may result from early defects in \(\beta\)-cell function. The 4% prevalence of diabetes and 18% prevalence of IGT in the offspring of type 2 diabetic parents is four and nine times greater, respectively, than that in the general population, which is estimated to be 1 and 2% in urban Cameroon \((10)\).

In contrast to studies in Caucasians and Pima Indians \((7,8,17,18)\) that showed last-
Table 2—Early insulin secretion in normal offspring and control subjects compared with offspring and control subjects with IGT

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<tr>
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<th>Offspring*</th>
<th>Control subjects</th>
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<tr>
<td></td>
<td>NGT</td>
<td>IGT</td>
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<tr>
<td>n</td>
<td>53</td>
<td>13</td>
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<td>Fasting glucose levels (mmol/l)</td>
<td>4.6</td>
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<td>Fasting plasma insulin (mU/l)</td>
<td>4.9</td>
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<td>2-h plasma insulin (mU/l)</td>
<td>22.8</td>
<td>13.6</td>
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<tr>
<td>Early insulin secretion (mU/mmol)</td>
<td>37.1</td>
<td>10.3</td>
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*Three offspring had type 2 diabetes and were not included in the analysis.

NGT = normal glucose tolerance; IGT = impaired glucose tolerance.

Hyperglycemia and hyperinsulinemia in the offspring of parents with type 2 diabetes, suggesting a decreased peripheral glucose utilization, fasting hyperglycemia and normoinsulinemia were observed in this study. This result may suggest that there is already impaired insulin secretion in the offspring of type 2 diabetic parents in this population. It is known that fasting plasma glucose concentrations depend on the rate of hepatic glucose production and peripheral glucose utilization. Indeed, increased hepatic glucose production may be the major factor responsible for the fasting hyperglycemia of type 2 diabetes. On the basis of a similar finding in the only other African study (19), it would appear that offspring of African type 2 diabetic parents show early abnormalities of glucose homeostasis.

The offspring in the present study had normal fasting insulin concentrations, thus suggesting normal insulin sensitivity. However, the total insulin response to oral glucose, which accounts for approximately two-thirds of the variability in insulin-mediated glucose disposal, seems to be the best surrogate of insulin resistance (20), and this was low in the offspring in this study when the area under the insulin response curve during OGTT was calculated. Total area under the glucose response curve was high in the offspring and, coupled with the normal fasting insulin concentrations, suggests an abnormality of insulin secretion rather than action. Individuals with a genetic predisposition to type 2 diabetes show a reduced β-cell compensatory response to reduced insulin sensitivity associated with obesity (17,21). Our findings remained unchanged after adjustment for BMI, and there was no evidence of increased hepatic insulin extraction, since the insulin-to-C-peptide ratio was normal, which might affect the fasting insulin concentrations. We can therefore reasonably conclude that fasting insulin concentrations were normal in the offspring. Some studies have shown hyperinsulinemia in offspring of type 2 diabetic parents, but these findings were in Caucasians, most of whom were obese (17,18).

There was an abnormality of insulin secretion in the offspring of type 2 diabetic patients marked by a decreased early insulin secretion even in those with NGT. The extent of total insulin release (the sum of first- and second-phase secretion) is tightly regulated in normal individuals (22). A different situation applies in individuals at risk of developing diabetes. Those who are glucose tolerant but insulin resistant show normal or increased first- and second-phase insulin secretion (23). It has been suggested that the loss of the first phase of insulin secretion is the earliest detectable abnormality in patients who are destined to develop type 2 diabetes (24,25). In fact, the prevalence of both type 2 diabetes and IGT was high among the offspring, and those who had NGT also had a significantly lower early insulin secretion than the control population with NGT (P < 0.02). The consequences of insulin deficiency are fasting hyperglycemia and impaired early insulin secretion—both of which were observed more in the offspring of type 2 diabetic patients than in the control subjects.

A decrease in early-phase insulin response is not only a characteristic of definite diabetes, but it is also frequently observed in subjects with IGT who later develop type 2 diabetes (25). Previous studies have also suggested that a low insulin response to glucose might be a genetic marker for type 2 diabetes (26). The finding of low 15- and 30-min post–glucose load C-peptide concentrations in the offspring confirms the fact that insulin secretion and therefore β-cell function is impaired in these offspring of African type 2 diabetic parents. Further, both triglycerides and cholesterol concentrations were similar between offspring and the control population, which is contrary to other offspring studies in which abnormalities of lipid metabolism in association with insulin resistance are common (17,27). Indeed, a reduction in β-cell mass has been attributed to be the pathogenesis of type 2 diabetes in black South Africans (28), while insulin resistance has been implicated in Caucasians and Mexican-Americans (17,18,24). Moreover, in Pima Indians, a high-risk population with a 35% prevalence of diabetes, insulin resistance was found to be a major risk factor for the development of type 2 diabetes, but a low early insulin response to glucose was an additional but weaker risk factor (25). Thus, subjects with parents with type 2 diabetes show multiple abnormalities of glucose homeostasis early in life, and some of these traits differ among races, regardless of the status of parental diabetes (21–25,29).

Therefore, either insulin secretory defects precede the development of type 2 diabetes or insulin resistance is the primary stage in the development of diabetes. The young age of the offspring in this study and the fact that those with IGT had a significantly lower 2-h insulin level than those with NGT and control subjects may suggest some degree of early β-cell defects. It would therefore appear that insulin secretory defect precedes the development of type 2 diabetes in this African study. However, the paucity of data from this part of the world makes comparison difficult.

In conclusion, total glucose intolerance (diabetes and IGT) is more prevalent in the offspring of African type 2 diabetic parents, and this may be due to an underlying degree of β-cell impairment marked by reduced early-phase insulin secretion.

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