Differences in the Prevalence of Diabetes and Impaired Glucose Tolerance According to Maternal or Paternal History of Diabetes

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OBJECTIVE — To determine whether diabetes risk is influenced by which parent (a parental history of diabetes is a well-documented risk factor for NIDDM) is reported to have diabetes.

RESEARCH DESIGN AND METHODS — We compared the prevalence of NIDDM and IGT for 4914 subjects according to their parental history of diabetes (mother only, father only, both parents, neither parent). Subjects were drawn from the San Antonio Heart Study, a population-based survey of diabetes and cardiovascular risk factors conducted in Mexican American and non-Hispanic white individuals between 1979–1988.

RESULTS — Men with a parental history of diabetes had a higher prevalence of both NIDDM and impaired glucose tolerance than men reporting no parental history of diabetes. Prevalence was equally high regardless of which parent, or whether both parents, had diabetes. In contrast, in women, only a maternal history of diabetes was associated with a higher prevalence of NIDDM and impaired glucose tolerance. Virtually no difference in NIDDM prevalence was found between women with a paternal-only history of diabetes and women with no parental history of diabetes.

CONCLUSIONS — Results differed markedly between men and women. The reason for this sex difference is unclear. It may represent a measurement bias, a sex-specific environmental effect, or a genetic effect that is expressed or transmitted differently between the sexes.

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NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; IGT, impaired glucose tolerance; BMI, body mass index; WHO, World Health Organization; ANOVA, analysis of variance; OR, odds ratio; CI, confidence interval.

The propensity of NIDDM to cluster in families is well documented and has provided some support for a genetic basis to the etiology of this disease. Further evidence that genes play an important role in this disease is indicated by the high degree of concordance (60–90%) for NIDDM observed among monozygotic twins (1,2), by the marked racial and ethnic differences existing in the prevalence of NIDDM (3–6), and by the strong correlation between NIDDM prevalence and genetic admixture observed in hybrid populations (7–10). However, thus far, family studies have failed to provide strong evidence for simple Mendelian inheritance of this disease.

To investigate further the pattern of transmission of diabetes within families, we compared the prevalence of diabetes and IGT among subjects according to their parental history of diabetes. In particular, we investigated whether the risk of diabetes differed between subjects reporting a maternal history of diabetes and those reporting a paternal history. Subjects were ascertained from the San Antonio Heart Study, a population-based survey of diabetes and cardiovascular risk factors in Mexican Americans and non-Hispanic whites.

RESEARCH DESIGN AND METHODS

— A total of 5178 subjects 25–64 yr of age were examined during the baseline phase of the San Antonio Heart Study, which was conducted between 1979 and 1988. Subjects were recruited from three types of neighborhoods: low-income barrios, middle-income transitional neighborhoods, and high-income suburbs. Within each type of neighborhood, a random sample of households was identified and all age-eligible Mexican American and non-Hispanic white subjects residing in selected households were invited to receive an examination at our mobile clinic. Because of the age restrictions, very few participants within households were blood related (either sibling-sibling or

Table 1—*Selected characteristics of the study population*

	Mexican Americans		Non-Hispanic whites		*P* value	
	Men	Women	Men	Women	Sex	Ethnicity
n	1315	1804	801	994	—	—
Age (yr)	43.0	42.9	44.6	44.8	NS	<0.001
BMI (kg/m^2)	28.0	28.4	26.7	25.0	<0.001*	<0.001
Reporting diabetes history in						
Mother only (%)	15.9	18.9	8.6	9.3	0.03	<0.001
Father only (%)	11.2	10.4	5.9	7.8	NS	<0.001
Both parents (%)	3.6	4.7	0.9	0.9	NS	<0.001
Neither parent (%)	69.3	66.0	84.6	82.0	0.01	<0.001
Glucose tolerance status						
With NIDDM (%)	11.2	12.6	5.0	5.1	NS	<0.001
With IGT (%)	11.7	16.0	11.5	10.4	0.001†	<0.001‡
With either (%)	23.4	29.2	16.6	15.7	0.001†	<0.001

*Non-Hispanic whites only.
†Mexican Americans only.
‡Women only.

parent-offspring). The overall response rate was 65.3%. Details of the study design, sampling, and recruitment procedures have been described elsewhere (6,11,12).

Ethnicity was defined on the basis of a previously published algorithm that considers parental surnames and birthplaces; stated ethnicity of grandparents; and participant's preferred ethnic identity when it indicated a distinct national origin (13). The protocol was approved by the University of Texas Health Science Center Institutional Review Board; all subjects gave informed consent.

A physical examination was performed, which included measurement of height and weight. BMI was defined as weight/height (kg/m^2). Plasma glucose was measured from blood samples drawn after a 12-h fast (6), and a 75 g glucose-equivalent load (Koladex or Orangedex, Custom Laboratories, Baltimore, MD) was administered. A second blood sample was obtained 2 h later; diabetes was diagnosed according to the plasma glucose criteria of the WHO (fasting blood glucose value ≥140 mg/dl or a 2-h value ≥200 mg/dl) (14). Individuals who did not meet WHO criteria but who gave a history of diabetes and were currently taking either oral antidiabetic agents or insulin also were considered to have diabetes. Nondiabetic subjects who had a 2-h glucose value ≥140 mg/dl, but <200 mg/dl, were considered to have IGT (14). Total glucose intolerance was defined as either diabetes or IGT.

Subjects were asked if either of their parents had diabetes. On the basis of this information, subjects were classified for this report into 1 of 4 groups: subjects reporting that their mother, but not their father, had diabetes (n = 711); subjects reporting that their father, but not their mother, had diabetes (n = 460); subjects reporting that both parents had diabetes (n = 149); and subjects reporting that neither parent had diabetes (n = 3594).

A total of 264 subjects was excluded from these analyses. Reasons for exclusion included insufficient diagnostic information for diabetes (n = 131), possible IDDM (n = 22), and unknown diabetes status of one or both parents (n = 111). This report is thus based on a total of 4914 subjects.

Clinical characteristics of study subjects were compared according to ethnic group and sex. Differences between groups were compared by ANOVA (for age and BMI) and by χ^2 test (for parental history of diabetes and glucose tolerance status). The prevalence of each glucose intolerance end point was calculated separately for men and women, according to parental history group (mother only, father only, both parents, neither parent). ORs—adjusted for ethnicity and age—then were calculated by multiple logistic regression analysis (15). To determine whether the association between glucose intolerance in the proband and parental history of diabetes differed between the sexes, a model was also considered in which the sexes were pooled and a sex-times-parental history interaction term was included.

RESULTS — Selected clinical characteristics of the 4914 study subjects are shown in Table 1 according to ethnicity and sex. Mexican-American participants were, on average, 1.5 yr younger than non-Hispanic-white participants, and had a moderately higher BMI. Mexican-American subjects were almost twice as likely to report having either a mother or father with diabetes than were non-Hispanic white subjects. For example, 15.9% of Mexican-American men re-

Table 2—*Prevalence of diabetes, IGT, and total glucose intolerance according to sex, ethnicity, and parental history of diabetes*

Parental history of diabetes	Men			Women		
	Mexican American	Non-Hispanic white	*P* value for parental history*	Mexican American	Non-Hispanic white	*P* value for parental history
Distribution of Subjects (*n*)						
Neither	911	678	—	1190	815	—
Mother only	209	69	—	341	92	—
Father only	147	47	—	188	78	—
Both	48	7	—	85	9	—
Diabetes (%)						
Neither	7.7	3.5	—	11.1	4.2	—
Mother only	20.1	14.5	<0.001	17.0	14.1	<0.001
Father only	18.4	8.5	<0.001	11.2	3.8	0.98
Both	16.7	28.6	0.002	18.8	11.1	0.02
IGT (%)						
Neither	11.0	10.5	—	15.7	9.6	—
Mother only	13.9	16.9	0.07	18.3	16.7	0.06
Father only	11.8	19.6	0.23	11.4	10.8	0.25
Both	15.6	0.0	0.59	20.7	11.1	0.23
Total glucose intolerance (%)†						
Neither	19.1	14.2	—	27.3	13.9	—
Mother only	34.5	32.3	<0.001	36.0	31.1	<0.001
Father only	30.6	28.3	<0.001	23.2	14.9	0.35
Both	32.6	28.6	0.01	40.2	22.2	0.009

*P value was calculated by comparing disease prevalence in each parental history category to disease prevalence in category with neither parent affected. *P* values adjusted for ethnicity by Mantel-Haenszel.

†The percentages for diabetic and IGT do not equal the percentage of total glucose intolerance because of missing 2-h glucose values on 197 patients whose fasting glucose values were < 110 mg/dl. These patients, all of whom denied a history of diabetes, were considered nondiabetic for these analyses but were excluded from the analyses of IGT and total glucose intolerance.

ported a mother with diabetes compared with 8.6% of non-Hispanic-white men; and 18.9% of Mexican-American women reported a mother with diabetes compared with 9.3% of non-Hispanic-white women (combined $P < 0.001$). Similarly, Mexican-American subjects were more likely to report a father with diabetes than were non-Hispanic-white subjects (11.2 vs. 5.9% for men, 10.4 vs. 7.8% for women; $P < 0.001$).

Table 2 shows the prevalence of diabetes, IGT, and total glucose intolerance according to sex, ethnicity, and parental history group. The prevalence of each end point was higher in men reporting any parental history of diabetes than in men reporting that neither parent had diabetes. For example, the prevalence of total glucose intolerance was 19.1% in Mexican-American men reporting that neither parent had diabetes compared with 34.5, 30.6, and 32.6% in Mexican-American men reporting a mother with diabetes, a father with diabetes, or both parents with diabetes, respectively. In non-Hispanic-white men, the corresponding prevalence rates for total glucose intolerance were 14.2% in men reporting no parental history of diabetes; and 32.3, 28.3, and 28.6% in men reporting a mother with diabetes, a father with diabetes, and both parents with diabetes, respectively. These differences were all statistically significant ($P \leq 0.01$).

The relationship between parental diabetes history and glucose intolerance was different in women and men. In particular, the prevalence of all categories of glucose intolerance tended to be higher in women reporting either a mother with diabetes or both parents with diabetes than in women reporting either a father or neither parent with diabetes. Little difference in disease prevalence was observed between subjects reporting a diabetic mother and those reporting both parents with diabetes or between subjects reporting a diabetic father and those reporting no parental history of diabetes. In Mexican-American women, the prevalence of total glucose intolerance was 36.0% in women with a diabetic mother and 40.2% in women reporting both parents with diabetes, compared with 23.2% in women reporting a father with diabetes and 27.3% in women reporting no parental history of diabetes. The corresponding prevalence

Table 3—*ORs, adjusted for ethnicity and age, comparing the odds of glucose intolerance (diabetes, IGT, or total glucose intolerance) between subjects with a parental history of diabetes and subjects without a parental history of diabetes*

	Men		Women		*P* value for sex* parental history interaction
	OR	(95% CI)	OR	(95% CI)	
Diabetes					
Parental history of diabetes					
Neither	1.00*		1.00*		
Mothers only	3.44	(2.32–5.12)	2.03	(1.47–2.81)	0.05
Fathers only	3.49	(2.16–5.64)	1.35	(0.83–2.19)	<0.01
Both	3.73	(1.72–8.08)	2.59	(1.41–4.77)	NS
Mother only vs. father only	0.95	(0.56–1.63)	1.59	(0.96–2.65)	NS
IGT					
Parental history of diabetes					
Neither	1.00*		1.00*		
Mother only	1.73	(1.16–2.59)	1.45	(1.08–1.95)	NS
Father only	1.89	(1.17–3.04)	0.84	(0.55–1.28)	<0.05
Both	1.73	(0.74–4.09)	1.70	(0.97–2.99)	NS
Mother only vs. father only	0.94	(0.53–1.66)	1.76	(1.09–2.84)	NS
Total glucose intolerance					
Parental history of diabetes					
Neither	1.00*		1.00*		
Mother only	2.42	(1.77–3.32)	1.73	(1.35–2.21)	NS
Father only	2.54	(1.74–3.69)	0.98	(0.70–1.38)	<0.01
Both	2.55	(1.35–4.83)	2.10	(1.32–3.36)	NS
Mother only vs. father only	0.94	(0.60–1.46)	1.77	(1.21–2.60)	<0.05

*Reference group.

rates in non-Hispanic-white women were 31.1 and 22.2% in women with a maternal history of diabetes and women reporting both parents affected, respectively; and 14.9 and 13.9% in women reporting a paternal history of diabetes and women reporting no parental history of diabetes, respectively.

ORs were calculated to determine the magnitudes of the associations between glucose intolerance and parental history of diabetes (parental history present versus absent). Neither sex had evidence that the ORs differed between Mexican Americans and non-Hispanic whites; therefore, the ethnic groups were pooled for these analyses. Table 3 presents age and ethnicity-adjusted ORs, which show associations between glucose intolerance and parental history of diabetes. In men, the ORs were very similar across all parental history categories—ranging from 3.44 to 3.73 for diabetes, 1.73 to 1.89 for IGT, and 2.42 to 2.55 for total glucose intolerance. In women, however, the ORs were elevated only among those with a maternal history of diabetes or both parents affected. The adjusted ORs for women with a paternal history of diabetes were 1.35 for diabetes, 0.84 for IGT, and 0.98 for total glucose tolerance. In no case did these ORs differ statistically from 1.0.

Within each sex, an OR was also computed comparing the odds of glucose intolerance between subjects with a maternal history of diabetes and those with a paternal history of diabetes. In men, essentially no difference in disease prevalence was found between these two groups, with the adjusted OR equal to 0.94 for each end point. Compared with women with a paternal history of diabetes, however, women with a maternal history of diabetes were more likely to have diabetes (OR = 1.59; $P = 0.07$), IGT (OR = 1.76; $P = 0.02$), and total glucose intolerance (OR = 1.77; $P < 0.01$). Inclusion of a sex-times-parental history interaction term in the logistic regression models indicated that the effect of a paternal history of diabetes on each glucose intolerance end point differed significantly between the sexes.

CONCLUSIONS — Under a simple familial aggregation model, the expectation is that any parental history of diabetes would be associated with diabetes. In these data this expectation was observed among males, but not among females. In the women, diabetes prevalence was elevated in those with a maternal history of diabetes (either with or without a paternal history of diabetes), but not in those with a paternal-only history of diabetes. The lack of an association between diabetes and paternal history of diabetes in

women was consistent across both ethnic groups and for both diabetes and IGT.

Several factors could account for these observations. First of all, the lack of an association between paternal history of diabetes and diabetes prevalence in women could be an artifact attributable to reporting bias. A major limitation of this study is that parents of the study subjects were not examined to confirm reported diabetes status. As a result, two potential sources of measurement error are introduced: first, subjects may be unaware of diagnosed diabetes in their parents; and, second, parents may have undiagnosed diabetes. How either of these sources of error could result in a bias that masks a "true" association between paternal diabetes and diabetes in daughters, but does not mask it in sons, however, is unclear. One could hypothesize, for example, that daughters are less likely to be aware of their fathers' diabetes status than their mothers' because fathers are more likely to have been undiagnosed. However, it would be surprising if this same differential awareness was not found in sons. In fact, because the frequency of reported parental diabetes in this study is higher in women than men (Table 1), a reporting error may be suspected to be more common in men. Alternatively, it may be that fathers are more likely to have undiagnosed diabetes than mothers; but, again, this alone would be insufficient to produce the observed patterns, as this likely would result in both daughters and sons underreporting the frequency of diabetes in their fathers. Finally, if a reporting bias does exist, it is unlikely to be produced by diabetic subjects being more likely to know the diabetes status of their parents than nondiabetic subjects, because the same pattern of associations of parental history also are present for IGT, a condition the patient is usually unaware of.

Aside from a reporting bias, other explanations must also be considered. The transmission patterns observed in men, for example, (i.e., increased prevalence of diabetes in all parental history groups) are consistent with an increased diabetes risk caused by either shared environmental exposures (e.g., diets, patterns of physical activity, similar lifestyles) or simple Mendelian patterns of inheritance (single gene or polygene). The transmission patterns observed in women, however, are consistent with a maternal-only pattern of inheritance. An environmental model that allows for a sex-specific parental effect of diabetes could also be proposed. For example, a maternal history of diabetes could be associated with diabetes in both sexes if one hypothesizes that the environment shared between mothers and both their male and female offspring is associated with diabetes risk. During their developmental years, for example, boys and girls may share diets and other important lifestyle variables with their mothers; and, in later life, these factors may lead to higher rates of diabetes among individuals with diabetic mothers than those with nondiabetic mothers. With regard to fathers, however, the shared environment may be sex-specific. For example, the shared environment between fathers and sons may be more important for future diabetes risk than the shared environments between fathers and daughters.

A second intriguing hypothesis that could explain the lack of an association between paternal history of diabetes and glucose intolerance in women is that women may be more likely than men to transmit diabetes to their offspring. Women with diabetes tend to give birth to larger babies than women without diabetes (16,17). In addition, the offspring of diabetic pregnancies tend to be more obese as children compared with the offspring of nondiabetic mothers (18,19). Freinkel (20) speculated that alterations in maternal-fuel availability occurring during the diabetic pregnancy may induce developmental defects in fetal tissue; and, in later life, these defects may be associated with a variety of adverse health outcomes, including insulin resistance and diabetes (21). This hypothesis was tested by Pettitt et al. (21), by comparing the prevalence of diabetes among subjects born to women who had diabetes during their pregnancy, subjects born to women with normal glucose tolerance during the pregnancy but who developed diabetes after delivery, and subjects born to nondiabetic women who did not subsequently develop diabetes. Diabetes prevalence was highest among the offspring of the diabetic mothers, intermediate among the offspring of the prediabetic mothers, and virtually absent in the offspring of the nondiabetic mothers.

Two difficulties arise with the intrauterine hypothesis as an explanation for the observed associations in this study. First, the intrauterine hypothesis is based on women having diabetes during their pregnancy. Although we did not ascertain the age of onset of reported diabetes in the parent, NIDDM is not generally diagnosed until the fifth decade or later (40 yr of age), or the fourth decade for Mexican Americans (22). Whether offspring of women with IGT are at increased risk of glucose intolerance is unknown. The second difficulty with the intrauterine hypothesis as an explanation for the current observations is that it does not readily explain the observed sex difference. An intrauterine effect should result in a maternal history of diabetes being more strongly associated with diabetes in both sexes, not just in women. Thus, one would have to hypothesize the presence of an additional modifying factor that would explain why paternal history of diabetes is as strongly associated with diabetes in men as a maternal history of diabetes.

In summary, the unexpected observation from this study was the sex interaction in which paternal history of diabetes was significantly associated with diabetes in men but not in women. The lack of association between paternal history of diabetes and diabetes in women could result from a measurement bias; however, it is not clear how such a bias would operate nor why it should operate in women but not in men. Alternatively,

this observation may reflect a true phenomenon related to parent-offspring transmission of sex-specific environmental effects.

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