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Is there an excess in maternal transmission of NIDDM?

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Summary Family studies have demonstrated that there is a strong genetic component to the aetiology of non-insulin-dependent diabetes mellitus (NIDDM), although the mode of inheritance is unknown. A number of recent family history studies, including one in Mexican Americans, have suggested that there is an excess of maternal transmission of NIDDM. Family history studies are subject to various types of bias, however, and the potential for bias in many of these studies has not been thoroughly evaluated. We therefore tested the hypothesis that diabetes is more likely to be transmitted from mothers than from fathers using data collected from a large family study of low-income Mexican Americans in San Antonio, Texas. The parents and offspring from 318 different nuclear families attended our medical clinic, where they received a 2-h oral glucose test. Diabetes was diagnosed on the basis of World Health Organization criteria. The sibships were classified into diabetic sibships (at least one sibling in the sibship was diabetic; $n = 54$) and non-diabetic siblings (no diabetic siblings; $n = 264$). The prevalence of diabetes among mothers of diabetic siblings was 61.4 % (27 of 44) compared to 64.3 % (18 of 28) among fathers of diabetic siblings (rate ratio = 0.95; 95 % confidence interval: 0.51–1.84). For the non-diabetic sibships, the prevalence of diabetes was 31.7 % (78 of 246) and 28.9 % (37 of 128) among mothers and fathers, respectively (rate ratio = 1.09; 95 % confidence interval: 0.73–1.67). These data provide no evidence for an excess maternal transmission of diabetes in Mexican Americans. [Diabetologia (1995) 38: 314–317]

Key words NIDDM, family studies, inheritance, genetics, Mexican Americans.

Non-insulin-dependent diabetes mellitus (NIDDM) is a common chronic disease that affects 6–7 % of adults in the United States [1]. The disease is diagnosed on the basis of elevated blood glucose levels and disease onset generally occurs in the fifth or sixth decade. Defects in both insulin sensitivity and insulin secretion are present in affected individuals, although the processes leading up to these abnormalities have not yet been clearly defined. One of the strongest risk factors for NIDDM is a positive family history for the disease, although elevated body mass index and low levels of physical activity also contribute to risk of the disease.

Surveys conducted in a variety of populations have noted that individuals with NIDDM are more likely to report a history of diabetes in the mother than in the father [2–8]. These observations have inspired a number of hypotheses to explain how diabetes could be preferentially transmitted through the maternal line, ranging from a gestational effect of diabetes on the fetus [9–11] to maternal inheritance of diabetogenic genes through mitochondrial DNA [12, 13].

Prior to pursuing hypotheses to account for differences between parents in the transmission of NIDDM, experimental verification of parental differences in NIDDM transmission is required. Nearly

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Abbreviations: NIDDM, Non-insulin-dependent diabetes mellitus; OGTT, glucose tolerance test; IDDM, insulin-dependent diabetes

all of the available data on differential transmission are based on reported history of diabetes in the parents. The possibility that these studies could reflect a differential awareness that individuals have of their mothers' and fathers' true diabetes status has not been adequately addressed.

We have also reported an excess maternal transmission of NIDDM in Mexican Americans residing in San Antonio, Texas [6]. This observation was made on the basis that NIDDM prevalence, as diagnosed by World Health Organization criteria, was significantly higher among individuals reporting that their mother had diabetes than in individuals reporting that their father had diabetes. From this same population, we have now obtained a sample of 319 nuclear families and performed glucose tolerance tests on family members to diagnose diabetes. In the present paper we report that there is essentially no difference in diabetes prevalence between the mothers and fathers of diabetic offspring, nor between the mothers and fathers of non-diabetic offspring.

Subjects and methods

Study subjects. Families were identified to represent a sample of families from a low-income neighbourhood (barrio) in San Antonio, Texas. Two sets of probands were identified: one set ascertained without regard to their disease status (randomly ascertained probands; $n = 33$) and one set ascertained because they had been previously diagnosed with NIDDM in a population-based survey [14] (diabetic probands; $n = 29$). All first, second, and third degree relatives of the randomly ascertained and diabetic probands aged 16 years and over were invited to receive a medical examination at our medical clinic.

From the 62 extended pedigrees, a total of 318 sibships were identified in which at least one parent and one child were examined for diabetes. For purposes of the analyses presented in this report, the unit of analysis is a sibship. We defined a diabetic sibship as one in which diabetes was present in one or more siblings and a non-diabetic sibship as one in which diabetes was not present in any sibling. There were a total of 54 diabetic and 264 non-diabetic sibships in which at least one parent had been examined.

Diagnosis of diabetes. Participating subjects were invited to attend a medical clinic, where they received a medical history interview, a brief physical examination, and a 2-h oral glucose tolerance test. Blood samples were drawn, following a 12-h fast, for measurement of plasma glucose, and a second sample was drawn 2 h after ingestion of a 75-g glucose-equivalent load (Orangedex; Custom Laboratories, Baltimore, Md., USA). Plasma glucose concentrations were measured using an Abbott VP System (Abbott Laboratories, South Pasadena, Calif., USA), and diabetes was diagnosed according to the World Health Organization plasma glucose criteria (fasting plasma glucose ≥ 7.8 mmol/L (140 mg/dl) or 2-h plasma glucose ≥ 11.1 mmol/L (200 mg/dl) [15]. Subjects reporting that they were currently taking antidiabetic medications were also considered to have diabetes. Diabetic subjects on insulin therapy were excluded from the analysis if their age of onset was less than 30 years or if their age of onset was less than 40 years and their body mass index was less than 30 kg/m^2, since such individuals were considered to have possible insulin-dependent diabetes.

Table 1. Number of sibships according to number of parents examined

	Diabetic sibships[a]	Non-diabetic sibships
Number of sibships	54	264
Mother only examined	26	135
Father only examined	10	18
Both parents examined	18	111

[a] Sibship, diabetic if 1 or more siblings has diabetes; sibship, non-diabetic if no siblings have diabetes

Statistical methods

The "excess maternal transmission" hypothesis would predict that mothers of diabetic subjects would be more likely to have diabetes than fathers of diabetic subjects. To test this hypothesis we compared the prevalence of diabetes between mothers and fathers of diabetic sibships using the chi-square test. As a control, we also compared diabetes prevalence between mothers and fathers of non-diabetic sibships. Exact binomial confidence intervals were computed around the rate ratios [16].

Results

Table 1 shows the number of diabetic and non-diabetic sibships according to the number of parents who were tested for diabetes. The mother was examined in 44 of the 54 diabetic sibships (81.5 %), while the father was examined in 28 of them (51.8 %). Of the 10 unexamined mothers, eight were deceased, one could not be located, and one refused our invitation to participate in the study. Of the 26 unexamined fathers, 17 were deceased, five could not be located, and the remaining four refused our invitation to participate. Thus, 75.7 % of the living fathers (28 of 37) and 95.3 % of the living mothers (44 of 46) were examined. In the 264 non-diabetic sibships, 246 of the mothers were examined (93.2 %) compared to 128 of the fathers (48.5 %).

Clinical characteristics of the diabetic subjects are shown in Table 2. There were 54 diabetic offspring, 105 diabetic mothers (27 having diabetic offspring), and 55 diabetic fathers (18 having diabetic offspring). The mean age at diagnosis was 41.8 years in the offspring, compared to 52.1 years and 53.6 years, respectively, in the diabetic mothers and fathers. Slightly more than 60 % of the diabetic parents were taking antidiabetic medications, compared to approximately 51 % of the diabetic offspring. Diabetic mothers were somewhat more likely to be taking insulin than diabetic fathers, although this difference was not statistically significant ($X^2_3 = 5.72$; $p = 0.06$).

The prevalence of NIDDM among the parents of the diabetic and non-diabetic sibships is shown in Table 3. Among the diabetic sibships, the prevalence of

Table 2. Clinical characteristics of diabetic subjects

	Diabetic offspring	Diabetic mothers	Diabetic fathers
n	54	105	55
Current age (years)	45.2 ± 11.3[a]	59.4 ± 12.3	61.2 ± 11.6
Body mass index (kg/m^2)	32.7 ± 6.7	32.1 ± 6.8	31.0 ± 5.8
Age at diagnosis (years)	40.8 ± 10.9	52.1 ± 12.1	53.6 ± 13.6
% newly diagnosed	43 % (23)[b]	30 % (32)	31 % (17)
Current treatments			
% tablets	35 % (19)	39 % (41)	53 % (29)
% insulin	15 % (8)	24 % (25)	9 % (5)

[a] Mean ± standard deviation; [b] number affected in parentheses

Table 3. Prevalence of NIDDM in mothers and fathers of offspring with and without diabetes

Offspring status	Number of sibships	Mothers		Fathers	
		%	*n*	%	*n*
Diabetic	54	61.4	(27/44)	64.3	(18/28)
Non-diabetic	264	31.7	(78/246)	28.9	(37/128)

Rate ratios (mothers/fathers):
diabetic offspring: RR = 61.4/64.3 = 0.95
95 % confidence interval: 0.51–1.84
non-diabetic offspring: RR = 31.7/28.9 = 1.09
95 % confidence interval: 0.73–1.67

diabetes in the mothers was 61.4 % (27 of 44), while the prevalence in the fathers was 64.3 % (18 of 28), indicating that mothers were 0.95 times as likely to have diabetes as the fathers (95 % confidence interval: 0.51–1.84: $X^2 = 0.06$; $p = 0.81$). Among the non-diabetic sibships, the corresponding prevalence rates of diabetes were 31.7 % (78 of 246) and 28.9 % (37 of 128), corresponding to a rate ratio of 1.09 (95 % confidence interval: 0.73–1.67; $X^2 = 0.31$; $p = 0.58$).

Discussion

Studies performed in several populations have suggested a marked excess in mother-to-offspring transmission of NIDDM. Alcolado and Alcolado [3] assessed the parental diabetes history in NIDDM patients in Britain and found that 36 % of mothers were affected compared to only 15 % of the fathers. These results were nearly identical to those obtained from 536 NIDDM patients in the French CODIAB study, where a history of diabetes was present in 33.0 % of the mothers of NIDDM patients compared to only 17.1 % in the fathers [4]. An excess of maternal transmission of diabetes has also been reported in several other populations [4–7], including Hispanics [6, 7] and Chinese [5]. In the National Health and Nutrition Survey (NHANES II), a maternal history of diabetes was significantly associated with fasting glucose levels in women, although in men, a history of diabetes in siblings was a stronger predictor [8].

It has been postulated that mothers with diabetes during their pregnancy have an increased likelihood of transmitting diabetes on to their offspring. The "fuel-mediated teratogenesis" hypothesis, first proposed by Freinkel [17], posits that fetal development is compromised during the diabetic pregnancy in such a way that pancreatic beta cells are unable in later life to respond adequately to the challenges posed by insulin resistance. Considerable epidemiologic evidence supports this hypothesis, including the fact that offspring of diabetic pregnancies tend to be more obese and more glucose intolerant compared to age- and sex-matched control subjects [9–10] and that diabetes prevalence is higher in the offspring of mothers who were diabetic during their pregnancy than in offspring of mothers who became diabetic after their pregnancy [11].

Given the relatively late onset of NIDDM, it seems unlikely that diabetes during the pregnancy could account for the large excesses in maternal transmission of NIDDM reported in some populations. Although the prevalence of gestational diabetes per se was not assessed in the San Antonio Heart Study, only 5.3 % of women and 4.3 % of men between the ages of 25 and 45 years, i.e., the childbearing years, had diabetes [18]. In populations such as the Pima Indians, where diabetes occurs at younger ages, diabetes during pregnancy could account for a larger proportion of maternal transmission.

Other explanations for increased maternal transmission of diabetes have been proposed. Maternal inheritance of diabetes associated with mutations in mitochondrial DNA have been reported [12, 13, 19, 20]. In most of these cases, however, diabetes tends to be transmitted as part of a broader syndrome, and it seems unlikely that this mechanism plays a large role in the intergenerational transmission of NIDDM. Environmental factors may also play a role since mothers may be more likely than fathers to pass diabetes risk factors on to their children.

The possibility that biased reporting may produce a spurious excess in maternal transmission of NIDDM has not been adequately evaluated. Reporting bias is a major concern in family history studies

since individuals may be more likely to know about their mothers' health status than their fathers'. A second concern is that, since women utilize health care services more than men, more fathers may have had undetected diabetes. Finally, fathers of diabetic subjects may be more likely than mothers to die of insulin resistance-associated cardiovascular disease before either the clinical onset or diagnosis of NIDDM.

A limitation of the present study is that not all parents could be examined. If diabetic fathers were more likely to participate than non-diabetic fathers, then the prevalence of diabetes in the fathers would have been overestimated and a "true" maternal excess in diabetes would have been obscured. Approximately 50 % of the fathers of diabetic and non-diabetic sibships were examined compared to 81 % and 93 %, respectively, of mothers of diabetic and non-diabetic sibships. The examination rates among *living* parents of diabetic sibships, however, was 76 % for fathers and 96 % for mothers. Seventeen of the 26 unexamined fathers were deceased. Because diabetes is associated with increased mortality, it is likely that we have *under*estimated, rather than overestimated, the true prevalence of diabetes in fathers. (It should be noted, however, that the "true" prevalence of diabetes in the mothers may also have been underestimated since 8 of the 10 unexamined mothers were also deceased). These limitations notwithstanding, the response bias associated with the present study may be less than the potential reporting bias of other study designs in which parental diabetes status is determined by a history of diabetes as provided by the offspring.

In conclusion, the data presented in this report suggest that in at least some of the previous studies reporting an excess of maternal transmission of diabetes, the apparent excess could be attributed to reporting bias. In the San Antonio Heart Study, which represents the same population from which families for the present study were sampled, the prevalence of diabetes was higher in subjects who reported a diabetic mother than in those who reported a diabetic father, although subanalyses of these data suggested that mother-daughter transmission was more common than mother-son transmission [5]. On the other hand, when both parents and their offspring were actually tested for diabetes, no evidence for parental differences in the transmission of NIDDM is observed.

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