Maternal Effect and Familial Aggregation in NIDDM

The CODIAB Study

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Non-insulin-dependent diabetes mellitus (NIDDM) is known to have a strong genetic basis, but the mode of inheritance is still unknown. Recent studies have suggested that maternal inheritance is important; this complicates the transmission pattern of NIDDM. In our study, the familial aggregation of diabetes and the maternal effect were investigated through three generations. The CODIAB Study recruited 536 NIDDM patients between 35 and 74 years of age from 10 diabetes centers in France. Familial aggregation was confirmed: among 218 NIDDM patients, 66% had at least one diabetic relative. Mothers were implicated 2 times more frequently than fathers ($P < 0.001$). This maternal effect was confirmed because more diabetic cases were noted among maternal than paternal aunts and uncles ($P < 0.02$). When we considered the next generation, women had more diabetic offspring than men ($P < 0.01$). Other factors susceptible to modify the familial aggregation were considered. The maternal effect was not significantly related to the patients' ages ($P > 0.2$). The genetic component was more important when the diagnosis was made earlier, but the maternal effect was homogeneous ($P > 0.3$). In conclusion, we found a familial aggregation of diabetes that suggests a strong genetic component with a mode of inheritance that may be influenced by a maternal environment. *Diabetes* 43:63–67, 1994

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NIDDM, non-insulin-dependent diabetes mellitus; df, degrees of freedom.

Non-insulin-dependent diabetes mellitus (NIDDM) is known to have a strong genetic basis and is among the most common metabolic disorders, both in developed and developing countries. The genetics of NIDDM has led to different, sometimes contradictory results and the mode of inheritance is still unknown (1,2). Recently, the term multifactorial disease has been evoked for NIDDM. One of the main difficulties is to evaluate the genetic and the environmental components.

A strong genetic component in NIDDM has been suggested by a concordance rate of 60–90% in monozygotic twins (3–6).

Family studies (7–13) have confirmed these results: an excess of diabetes cases in siblings and first-degree relatives of diabetic patients compared with control subjects in case-control studies and in the general population, after adjustment for age and other parameters. Case-control studies have shown metabolic abnormalities (higher fasting concentration of glucose and higher insulin level) in children of NIDDM patients (14–19). Segregation analysis for insulin has shown the effect of a major gene regulating the insulin level in NIDDM pedigrees (20,21). This analysis presumes genetic defects are involved in NIDDM. Such results favor a strong genetic component in diabetes; however, molecular genetic studies have not been successful in finding disease markers, despite a large number of candidate genes. Several studies have suggested that the intrauterine environment is an important determinant of diabetes development (22–28). Such a maternal effect complicates the transmission pattern of NIDDM.

The main aim of this study was to clarify the mode of NIDDM transmission by using the family history of diabetes in NIDDM patients over three generations and to investigate the role of maternal inheritance. Other factors susceptible to modify familial aggregation or the maternal

TABLE 1
Diabetes in the family of NIDDM patients

Family relationship	*n*	Percentage with diabetes	Insulin-treated diabetes (%)	Non-insulin-treated diabetes (%)	Treatment not known (%)
Mother	488	33.0	4.9	24.8	3.3
		}$P < 0.001$*			
Father	443	17.1	2.7	11.0	3.4
Brother or sister	449	33.2	4.2	25.8	3.2
Maternal aunt or uncle	361	19.6	2.8	12.1	4.7
		}$P < 0.02$			
Paternal aunt or uncle	350	12.6	0.6	7.7	4.3
At least one relative	218	66.0	—	—	—

*Test of difference of frequencies for the maternal effect.

effect, such as age of patients, age of parents at death, and age at diabetes diagnosis in index patients, were considered.

RESEARCH DESIGN AND METHODS

Study group. CODIAB (a French study of diabetes complications) is a cross-sectional study that recruited 536 NIDDM patients from 10 diabetes centers. The geographical localization in France of the NIDDM patients was representative of different lifestyles, climates, and diet. Patients were 35–74 years of age and were either treated by diet and/or by hypoglycemic drugs for more than one year or needed insulin treatment for more than two years after diagnosis. Patients with secondary diabetes or other serious pathologies (for example, cancer or AIDS) were excluded.

Each patient was examined by a diabetologist. During the investigation, the patient answered the following question about diabetes for each member of her or his family (parents, aunts and uncles, siblings and offspring): "Do they have diabetes, is it insulin-treated or non-insulin-treated or is the treatment not known?" We considered only people for whom the diabetic state of their relatives was known (for siblings, aunts, and uncles). The data were reported on a genealogical tree.

Statistical analysis. The existence of a maternal effect can be tested over two generations. The first generation involved the index patients, their parents (mother versus father), and also their aunts and uncles (maternal versus paternal). The results obtained in this generation can be confirmed by the second-generation analysis, involving index patients (women and men) and their offspring. These three analyses are independent.

The homogeneity of the maternal effect between the index patient and her or his parents also was studied according to age at examination and age at diabetes diagnosis in the index patient. χ^2-tests were used for comparison of proportions, testing for homogeneity of odds ratios, and linearity of the age at diagnosis (29,30). All data are expressed as means ± SD.

For analyses, we used the SAS statistical package on the VAX 8530 computer at the INSERM computer center.

RESULTS

Frequency of diabetic relatives. Details about the family history of diabetes were available from a total of 536 patients (247 women and 289 men). For 218 patients, data were complete for parents, and the diabetic status was known for at least one sibling and one aunt or uncle on both the paternal and maternal sides of the family. Mean age at examination was 57.3 ± 9.3 years in women and 58.8 ± 8.8 years in men. The frequencies of index patients who reported having diabetic relatives (mothers, fathers, sisters, brothers, maternal aunts and uncles, and paternal aunts and uncles) are given in Table 1. In all cases, women and men were analyzed together because no evidence of a sex effect was noted, regardless of the family relationship considered (Table 2).

For these 218 NIDDM patients, 66% reported at least one diabetic family member, and among them, 46% had at least two; 33% of the patients had a diabetic mother, including 5% with insulin-treated diabetes, 25% with non-insulin-treated diabetes, and 3% with treatment unknown. In contrast, only 17% had a diabetic father: 3% with insulin-treated diabetes, 11% with non-insulin-treated diabetes, and 3% with treatment unknown. One third had at least one diabetic sister or brother. At least one diabetic aunt or uncle was noted on the maternal side in 20% and on the paternal side in 13% of the patients. In addition, almost 8% of patients had a diabetic offspring (2% insulin-treated, 5.5% non-insulin-treated, and 0.5% treatment unknown).

Maternal effect. Among index patients, 33% had a diabetic mother compared with 17% who had a diabetic father ($\chi^2 = 27$, df = 1, $P < 0.001$), showing a significant maternal effect (Table 1). About 20% of index patients had at least one diabetic aunt or uncle on the maternal side, 13% on the paternal side, ($\chi^2 = 6$, df = 1,

TABLE 2
Percentage of subjects with diabetic family members, according to the sex of the index NIDDM patient

Family relationship	Men (%, *n*)	Women (%, *n*)
Mother	34.2, 263	31.5, 225
Father	16.7, 239	17.6, 204
Brother or sister	30.7, 238	36.0, 211
Maternal aunt or uncle	18.7, 198	20.2, 163
Paternal aunt or uncle	12.8, 196	12.3, 154
Offspring	3.8, 235	11.1*, 215

*$P < 0.01$ for comparison of transmission by mother or father.

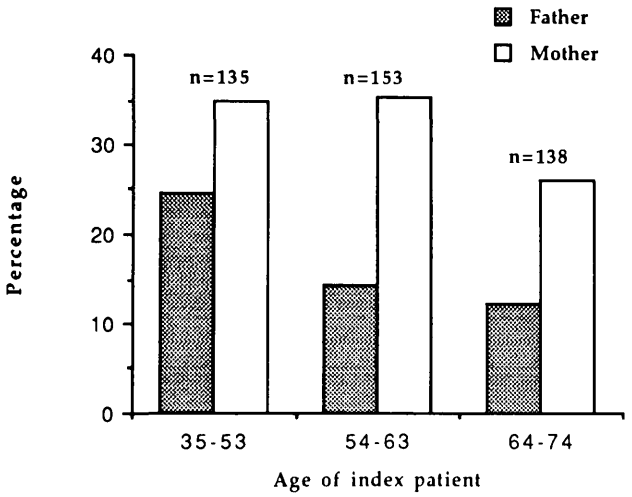

FIG. 1. Percentage of index patients with a diabetic mother or father, according to the age of the index patient. Nonhomogeneity of maternal effect among classes was not accepted: $P > 0.05$. Maternal effect: $P < 0.001$.

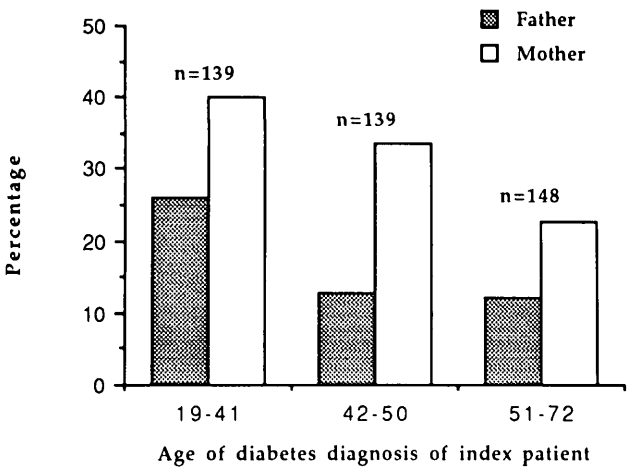

FIG. 2. Percentage of index patients with a diabetic mother or father, according to the age at diabetes diagnosis in the index patient. Nonhomogeneity of maternal effect among the three age-classes was not accepted: $P > 0.05$. Maternal effect: $P < 0.001$. In the age-class 19–41, 94% of patients were >25 years of age.

$P < 0.02$). Overall for this generation, 41 and 20% of diabetic patients had at least one diabetic family member on the maternal and paternal sides, respectively ($\chi^2 = 21$, df = 1, $P < 0.001$).

To confirm these results, we considered the frequency of diabetic offspring among diabetic men ($n = 235$) and women ($n = 215$); 3.8% of diabetic men had an affected offspring compared with 11.1% of diabetic women ($\chi^2 = 8$, df = 1, $P < 0.01$) (Table 2).

Age of patients. Data were available on the diabetic status of the mothers and fathers of 426 index patients. Figure 1 shows the percentage of patients with a diabetic mother or father, according to the age of the patient. The heterogeneity in maternal effect between the three age-classes was not significant ($\chi^2 = 3.0$, df = 2, $P > 0.2$).

In the youngest age-class, 135 diabetic patients knew the diabetic status of their mother and father: 35.8% had a diabetic mother, and 24.6% had a diabetic father ($\chi^2 = 3.5$, df = 1, $P < 0.07$). In the second age-class, which involved 153 patients, 35.3% had a diabetic mother, and 14.4% had a diabetic father ($\chi^2 = 18$, df = 1, $P < 0.001$). In the oldest group (138 patients), the percentages were 26.1 and 12.4%, respectively ($\chi^2 = 8.5$, df = 1, $P < 0.01$).

Age at diabetes diagnosis in index patients. The percentage of patients who had a diabetic mother decreased from 40.2 to 23.0% ($\chi^2 = 10$, df = 2, $P = 0.006$) as the age at diabetes diagnosis increased (Fig. 2). Similar results were obtained for patients with a diabetic father; frequencies decreased from 25.9 to 12.1% ($\chi^2 = 13$, df = 1, $P = 0.003$). These frequencies were not significantly different from a linear trend. The maternal effect was homogeneous over the three classes ($\chi^2 = 2.1$, df = 2, $P > 0.3$).

DISCUSSION

Family effect. The diabetic population that we studied was similar to that from other French studies. The mean age was close to 60 years, and the percentage of diabetic relatives treated with insulin was ~15% (31,32).

Of the diabetic patients enrolled in this study, 66% had at least one diabetic relative among their parents, aunts, uncles, siblings, or offspring. This frequency can be compared with the diabetes prevalence (2%) generally found in the French population (32). This result supports the familial aggregation of diabetes and suggests that a dominant mode of transmission could be involved as discussed by O'Rahilly et al. (1). This hypothesis was not confirmed by segregation analysis. Similar results have been reported in a number of others studies (7–13). Cheta et al. (13) found that among 300 NIDDM patients (mean age 57.1 years), 33% had a diabetic relative (parent, sibling, or offspring). In the Whitehall study (9,10), 30% of diabetic cases had an NIDDM family member (parent or sibling), compared with 57% found in this study. Baird (12) found that 10% of the siblings of 238 NIDDM patients had diabetes, a much lower frequency than the 32% in this study. Because the parents of younger diabetic patients may not have yet developed diabetes, our figure of 66% may be an underestimate. Diabetes is well known to be a familial trait; thus diagnosis is often evoked based on not only clinical and biological signs but also a family history of diabetes. This will introduce an overestimation of the familial component.

Maternal effect. A significant maternal effect was noted in two generations and in two branches in the one generation, even though diabetes prevalence was higher in men than in women in other French studies in all age-groups (31,32). These results confirm those found by others who investigated the maternal effect (22–28). Alcolado et al. (22) assessed the family history of diabetes in NIDDM patients. The number of cases of diabetes among mothers and fathers was noted for each patient. They reported that mothers were implicated in significantly more cases (36% in mothers, 15% in fathers). The age of those subjects was comparable to those in our

study group, and the percentages (36 and 15%) are similar to ours, 33 and 17%, respectively. In the Pima Indians, Pettitt et al. (23) found a higher prevalence of diabetes among offspring (20–24 years of age) of NIDDM women (45%) than in offspring of nondiabetic women (1.4%) or offspring of prediabetic women (8.6%). This can be compared with the 12% of diabetic women in our study, who had at least one diabetic offspring. The authors suggested that the intrauterine environment is important for the development of diabetes. Dörner et al. (26) found that familial diabetes on the maternal side was 2.54-fold more frequent than on the paternal side in diabetic patients with diabetes onset at ≥25 years of age. Data from a study of patients with gestational diabetes showed that 33% of the patients had diabetic mothers and 8.8% had diabetic fathers (27).

Possible biases in this study. A number of possible explanations exist for the higher frequency of diabetes among mothers compared with fathers.

In France, women on average live longer than men (33). This could explain an excess of mothers of index patients who developed diabetes, particularly in the first generation (parents). Whereas in our population, the mean ages of fathers and mothers at death were not significantly different (67.1 ± 14.4 and 68.9 ± 15.6 years, respectively), significantly more deaths occurred among fathers (90%) than mothers (72%), which would be partly attributable to the two World Wars. The age of living parents was not available, so we were not able to test the hypothesis that mothers had more time to develop diabetes. Another hypothesis is that men are detected with diabetes less often than women; this would explain an excess of diabetic mothers but contradicts the fact that screening is probably more common in men (32) and confirms the maternal effect. A third explanation for this maternal effect is that women develop diabetes earlier than men; this was not the case in a French study (32) but has been observed in Italy (34). Although the above may explain the maternal effect in parents, it does not explain the maternal effect found among aunts and uncles, nor among the offspring. We cannot reject, however, the hypothesis that mothers may have more knowledge about the diabetic state of their offspring and that both female and male diabetic patients may have more knowledge about their mothers and their maternal aunts and uncles.

Etiology of the maternal effect. True genetic maternal autosomal inheritance may result if genes are expressed in the uterine maternal environment, during ontogeny, or if maternally derived genes are passed on to offspring in preference to paternal genes (mitochondrial heredity). It has been suggested that the intrauterine environment may play a role in the transmission of NIDDM (23) and that poor fetal and early postnatal nutrition is a risk factor for NIDDM (25). These studies favor the existence of genes whose expression is a result of an interaction with the maternal environment. Evidence for mitochondrial heredity has been found by Ballinger et al. (24), who found a maternally transmitted diabetes associated with a 10.4 mitochondrial DNA deletion. More recently, Reardon et al. (28) found a point mutation affecting position 3243 in the tRNA leucine mitochondrial gene.

Age of patients and age at diabetes onset. The frequency of diabetic mothers was similar whatever the age of the patient, and although the maternal effect was homogeneous over the three classes, it was least evident in the youngest age-class ($P < 0.006$). The mothers, however, are likely to be younger than the fathers and may not have developed diabetes yet.

We found that the genetic component was lower when diabetes onset was late. Our results confirm those of Simpson (7), who showed that the severity of diabetes and the age at diabetes onset were genetically determined. They concluded that this might explain the mode of transmission of NIDDM and that environmental factors were more important when diabetes onset was late. However, whatever the age at onset, the maternal effect was homogeneous in our data, in contrast with Dörner et al. (26), who showed a positive correlation between the maternal effect and age at diagnosis.

Conclusion. NIDDM has a strong genetic component and an autosomic dominant mode could be involved. In our study, the familial component was more important when the disease was diagnosed at an earlier age, and it was influenced by a maternal environment, as seen in three branches of the genealogical tree. To confirm our results, a prospective study is required to follow up the offspring of diabetic patients; more precise details about the age at diagnosis and the age and status of parents would be necessary. Genes coded by mitochondrial DNA should be investigated to elucidate the molecular origin of the maternal effect.

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APPENDIX: CODIAB-INSERM-ZENECA STUDY GROUP PARTICIPATING CENTERS

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