Familial Clustering of Diabetic Nephropathy in Brazilian Type 2 Diabetic Patients

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There is evidence for genetic predisposition to diabetic nephropathy in type 1 diabetic patients. However, there are few studies on type 2 diabetic patients, and most of those have been conducted on ethnic minorities or Caucasian individuals. The aim of this study was to ascertain the presence of an inherited predisposition to diabetic nephropathy in a sample of Brazilian type 2 diabetic patients. Families with two or more type 2 diabetic siblings were identified. Subjects with the longest duration of known diabetes were considered probands. Some 90 probands and their 107 diabetic siblings were studied. Urinary albumin excretion rate was measured in a sterile 24-h urine sample on at least three different occasions. Probands and siblings were classified according to urinary albumin excretion rate as normo- (<20 µg/min), micro- (20–200 µg/min), or macroalbuminuric (>200 µg/min). Patients with end-stage renal disease were included in the macroalbuminuric group. Macroalbuminuria was identified in 5.2% of the siblings of normoalbuminuric probands and in 24.1% of the siblings of macroalbuminuric probands (P = 0.024). In multiple logistic regression, the presence of diabetic nephropathy in probands (micro- or macroalbuminuria and end-stage renal disease) was significantly associated with the presence of sibling diabetic nephropathy (odds ratio = 3.75, 95% CI = 1.36–10.40, P = 0.011) adjusted for proband fasting plasma glucose and diabetes duration. Interpretation of these results should take into account the possibility that the families including siblings with diabetic nephropathy may have been overcounted and, on the other hand, that the siblings without diabetic nephropathy may have been undercounted. In conclusion, there is a familial aggregation of diabetic nephropathy in this sample of type 2 diabetic patients. ***Diabetes*** **48:909–913, 1999**

Familial clustering of diabetic nephropathy (DN) has been described in type 1 diabetic patients (1–3). The presence of DN in a type 1 diabetic patient increases by almost three times the risk that a diabetic sibling will present an abnormal urinary albumin excretion rate (UAER). This marked effect is compatible with the presence of a gene that has a major effect that predisposes to the development of DN (4). There is some evidence suggesting that this genetic effect might also be related to a predisposition to essential hypertension and cardiovascular disease (4–8).

This clustering was also observed in genetically homogeneous groups of type 2 diabetic patients, such as the American Pima Indians (9) and Caucasian individuals from Italy (10). The presence of this association in another population will further support the role of genetic predisposition in the pathogenesis of DN.

Therefore, the aim of this study was to analyze the familial clustering of DN in type 2 diabetic patients in different stages of diabetic renal disease.

RESEARCH DESIGN AND METHODS

Subjects. Families with two or more siblings with type 2 diabetes were identified through two processes: *1*) patients attending the Endocrine Division and Dialysis Unit of Hospital de Clínicas de Porto Alegre between March 1994 and March 1997 (~3,000 patients) were asked about the presence of a sibling with diabetes and *2*) patients with type 2 diabetes who had a sibling with type 2 diabetes were recruited through an advertisement published in a local newspaper; the advertisement did not mention renal disease. During the ascertainment process, the renal status of patients not on dialysis was not known. Considering that the prevalence of diabetes in the siblings of type 2 diabetic patients is around 17% (11), we expected to identify ~510 families with at least two siblings with diabetes. Only families with members with known diabetes duration of at least 5 years were included. In ~30% of the families seen at the outpatient clinic, at least one of the siblings had a known diabetes duration of <5 years, and these families were excluded. After excluding families with only one offspring (10%) and with type 1 diabetic members (10%), we expected to have 255 eligible families. There were 149 families identified. We believe that the difference between the expected number of families and the number of families that was actually identified was due to sibling underreporting or to patients being unaware of the presence of diabetes in the sibling. This is supported by the fact that 48% of type 2 diabetic patients are undiagnosed (12). Of the 149 families identified, 59 were excluded for several reasons: 26 siblings lived outside the state of Rio Grande do Sul; five male patients had cardiac failure, metastatic prostate cancer, persistent urinary tract infection after prostate surgery, hepatic cirrhosis, and alcoholism; and in 28 families, the diabetic sibling was not available for study (11 refused to participate and 17 siblings were deceased at the time of the study).

The subject with the longest known duration of diabetes was considered the proband. The probands excluded from the study because of unavailable siblings did not differ from the probands included in the study in terms of clinical and renal status (52.8% male; mean age 57.8 years; diabetes duration 10.8 years; 63% normo-, 24% micro-, 13% macroalbuminuric). A total of 90 probands (12 from the newspaper advertisement, 8 from the Dialysis Unit, and 70 from the outpatient clinic) and their 107 siblings were analyzed. In 14 families, there was more than one sibling with diabetes.

Among the patients attending this hospital, 84% were from the metropolitan area of Porto Alegre. The city of Porto Alegre is the capital of Rio Grande do Sul, the southernmost state in Brazil. According to the last demographic census (13), the metropolitan area has 594,106 inhabitants who are older than 30 years. The prevalence of type 2 diabetes in the general population is 8.8% (not previously diagnosed = 4.2%) (12). The Endocrine Division provides medical assistance to ~12% of this known diabetic population. Furthermore, 86% of the state population is classified as white, 8.4% as mulatto, 4.0% as black and 0.9% as native, yellow, or not defined (classification based on self-reporting) (13). The patient population of this center reflects this ethnic distribution.

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ANOVA, analysis of variance; CV, coefficient of variation; DN, diabetic nephropathy; ESRD, end-stage renal disease; OR, odds ratio; UAER, urinary albumin excretion rate.

The diagnosis and the type of diabetes were established according to World Health Organization criteria and specific drug treatment. Patients were considered to have type 2 diabetes based on the following criteria: diagnosis of diabetes after 30 years of age, non-insulin treatment during the first 5 years after diagnosis, and absence of episodes of ketoacidosis. The study protocol was approved by the Ethics Committee at the Hospital de Clínicas de Porto Alegre. All patients gave their written informed consent to participate.

Patient evaluation. Patients answered a standard questionnaire that included questions about age, age at diabetes diagnosis, smoking habits, skin color (white, black, or mulatto), and drug treatment. They underwent a complete physical examination and laboratory tests. Patients were weighed in light outdoor clothes without shoes, and height was recorded. BMI was calculated as weight (in kilograms) divided by height (in meters) squared.

Sitting blood pressure was measured twice after a 10-min rest to the nearest 2 mmHg, using a standard mercury sphygmomanometer (phases I and V of Korotkoff sounds). Hypertension was defined as blood pressure ≥140 mmHg (systolic) and/or ≥90 mmHg (diastolic), or any value when antihypertensive drugs were in use (14).

Fundus examination was performed by an ophthalmologist after mydriasis. The findings were graded as: *1*) no signs of diabetic retinopathy, *2*) nonproliferative retinopathy (microaneurysms, hemorrhages, hard exudates), or *3*) proliferative retinopathy (newly formed blood vessels and/or fibrous tissue into the vitreous cavity). Smokers were defined as those smoking at the time of the study. Exsmokers were defined as those who had smoked for ≥1 year and had quit for at least 1 year.

The probands and the siblings had a 10-ml blood sample collected after 12 h of fasting. Glucose was measured by the glucose-oxidase method, GHb electrophoresis by a boronate affinity binding assay (IMX; Abbot Laboratories, Chicago) (normal range: 5.3–7.5%, interassay coefficient of variation [CV] 6.5%), creatinine by Jaffé's reaction, and cholesterol and triglycerides by a colorimetric method. Urinary albumin was measured by radioimmunoassay (DPC, Los Angeles, CA) (inter- and intra-assay CV = 2.3 and 2.8%, respectively) in 24-h timed sterile urine samples at least three times over a 3-month interval. ACE inhibitors were withdrawn for a week before UAER measurements. The probands and siblings were classified as normoalbuminuric (UAER < 20 μg/min), microalbuminuric (UAER 20–200 μg/min), or macroalbuminuric (UAER > 200 μg/min), or as patients with end-stage renal disease (ESRD). The macroalbuminuric patients and those with ESRD were analyzed together. DN was diagnosed in the outpatients by the presence of micro- or macroalbuminuria (increased UAER in two of three urine samples) without evidence of kidney or renal-tract disease other than DN (urinary tract infection, hematuria, abnormal urinary sediment, and/or elevated plasma creatinine without proteinuria) (15). In the dialysis group, a diagnosis of DN was assumed when proteinuria, hypertension, and diabetic retinopathy were present and there was no evidence of other renal disease.

Statistical analysis. χ^2, Fisher's exact test, one-way analysis of variance (ANOVA), Kruskal-Wallis's ANOVA, and Student's t test were used to compare clinical and laboratory characteristics among probands or among siblings. Data from the siblings were grouped according to proband renal status. Differences between groups were assessed using the Tukey test for continuous data. In the categorical data, differences among the groups were identified by adjusted residual values >1.96 (16). Continuous data were expressed as means ± SD or as medians (range). A P value (two sided) <0.05 was considered to be significant. The risk of DN in the proband was calculated as an odds ratio (OR). The relationship of clinically relevant variables to proband renal status was assessed by a multiple logistic regression analysis with proband DN as the dependent variable. Statistically significant variables in the univariate analysis were included in the model. The final model was constructed using the forward stepwise Wald method ($P \leq 0.10$). All calculations were performed using the STATA and SPSS statistical packages.

RESULTS

Proband data. The clinical and laboratory characteristics of the probands (n = 90) are reported in Table 1. There were 49 normo-, 18 micro-, and 23 macroalbuminuric probands. The normo-, micro-, and macroalbuminuric groups were similar regarding sex, ethnic distribution, age, known diabetes duration, and BMI. Insulin was used in 14.3% of the normo-, 33.0% of the micro-, and 39.1% of the macroalbuminuric probands (P = 0.045). Blood pressure levels, prevalence of hypertension, and proportion of probands using antihypertensive drugs were also similar among the groups. ACE inhibitors were used by 12.2% of the normo-, 11.1% of the micro-, and 8.7% of the macroalbuminuric probands (P = 0.905). The prevalence of diabetic retinopathy was higher in the groups with micro- and macroalbuminuria. The microalbuminuric group had higher levels of mean GHb than the normo- and macroalbuminuric groups, and creatinine levels were increased in the macroalbuminuric group as expected. Fasting plasma glucose and lipid profiles were similar among groups (data not shown).

When the probands were grouped according to the presence of DN (micro- or macroalbuminuric or dialysis, n = 41) or absence of DN (normoalbuminuric, n = 49), the groups differed in mean age (59 vs. 55 years, P = 0.043), diabetes duration (14 vs. 11 years, P = 0.046), and metabolic control (plasma glucose levels: 12.93 vs. 10.99 mmol/l, P = 0.049; and GHb: 8.73 vs. 6.85%, P = 0.018). The groups did not differ regarding sex proportion, mean blood pressure, cholesterol, or triglyceride levels.

Sibling data. Table 2 reports the clinical and laboratory characteristics of the siblings according to proband renal status. Among the 107 siblings evaluated, 52.7% were normo-, 18.2% were micro-, and 26.4% were macroalbuminuric. The sibling groups were similar regarding sex, age, known diabetes duration, BMI, and presence of retinopathy. Insulin was used in 12.1% of the siblings of normo-, 20% of the siblings of micro-, and 10.3% of the siblings of macroalbuminuric probands (P = 0.580). Blood pressure levels, prevalence of hypertension, and proportion of siblings using antihypertensive drugs were similar among the groups. ACE inhibitors were used by 22.4, 15.0, and 10.3% of the siblings of normo-, micro-, and macroalbuminuric probands, respectively (P = 0.368). Blood glucose levels and lipid profile did not differ among groups (data not shown). The median UAER was higher among the siblings of micro- and macroalbuminuric subjects than for the siblings of normoalbuminuric patients (P = 0.011).

DN clustering. Table 3 shows the distribution of DN in the sibling group according to proband renal status. Only 5.2% of the siblings of normoalbuminuric probands had macroalbuminuria, while 24.1% of the siblings of macroalbuminuric probands were also macroalbuminuric. The siblings of microalbuminuric probands had an increased proportion of both micro- and macroalbuminuria, but this was not statistically significant. DN (micro- and macroalbuminuria) was present in 25.9% (n = 15) of the siblings when the probands were normoalbuminuric, in 50.0% (n = 10) when the probands were microalbuminuric, and in 55.2% (n = 16) when they were macroalbuminuric. This familial clustering of DN was present even when only the probands and siblings with a diagnosis of diabetes for at least 10 years were analyzed (P = 0.012).

The presence of DN (micro- and macroalbuminuria) in the proband tripled the chance of DN in the sibling (OR = 3.24, 95% CI = 1.34–7.95, P < 0.01). When only the normo- and macroalbuminuric probands were considered, this risk markedly increased (OR = 7.72, CI = 1.48–45.01, P < 0.01). These values were influenced by the close agreement between normoalbuminuric probands and normoalbuminuric siblings. The future development of DN in the group of normoalbuminuric siblings could decrease the magnitude of the effect of familial clustering. However, the diabetes duration of the normoalbuminuric siblings of normoalbuminuric probands was similar to the diabetes duration of the normoalbuminuric siblings of micro- and macroalbuminuric probands (6.8 ± 3, 7.8 ± 2, and 7.0 ± 3 years, respectively, P = 0.652). The prevalence of retinopathy was also similar among the normoalbuminuric siblings of the normo-, micro-, and macroalbuminuric probands (25, 46, and 35%, P = 0.431).

TABLE 1
Clinical and laboratory characteristics of type 2 diabetic probands grouped according to stage of DN

Proband characteristics	Proband renal status			*P*
	Normoalbuminuric	Microalbuminuric	Macroalbuminuric	
n	49	18	23	—
Sex (male)	29.0	38.9	56.5	0.074
White (%)	83.7	77.8	82.6	0.854
Age (years)	55.0 ± 8.0 (39–72)	58.3 ± 11.6 (41–81)	60.0 ± 9.9 (45–80)	0.127
Diabetes duration (years)	11.9 ± 6.1 (5–30)	12.9 ± 10.2 (5–40)	15.6 ± 8.1 (5–32)	0.138
BMI (kg/m^2)	27.8 ± 4.5 (18–42)	28.5 ± 2.7 (24–32)	28.9 ± 5.6 (21–42)	0.690
Systolic blood pressure (mmHg)	153.8 ± 23.0 (92–200)	155.1 ± 22.3 (100–193)	157.8 ± 23.6 (100–196)	0.506
Diastolic blood pressure (mmHg)	93.7 ± 14.2 (60–120)	91.0 ± 13.8 (66–120)	93.3 ± 19.1 (60–128)	0.859
Hypertension	71.4	77.8	78.0	0.773
Antihypertensive treatment*	60.0	64.0	61.1	0.962
Retinopathy	42.5	88.9	87.0	< 0.001†
Insulin use	14.3	33.0	39.1	0.045†
GHb (%)	7.09 ± 2.14 (4.7–11.6)	9.33 ± 2.14 (5.3–11.4)	7.80 ± 1.29 (6.3–9.3)	0.040‡
Creatinine (μmol/l)	76.02 ± 14.14 (53.04–106.08)	82.21 ± 22.98 (53.04–114.92)	292.60 ± 340.34 (53.04–1,060.8)	< 0.001§
UAER‡ (μg/min)	6.39 (0.76–19.0)	43.70 (21.0–187.57)	626.64 (202.45–2,400)	—

Data are % or means ± SD (range). *P* values are by χ^2 or ANOVA. *All antihypertensive agents included. †Normoalbuminuric group vs. micro- and macroalbuminuric groups; ‡micro- vs. normo- and macroalbuminuric groups; §normo- and micro- vs. macroalbuminuric group.

This evidence suggests that the normoalbuminuric siblings are a homogenous group in relation to the length of exposure to hyperglycemia and other microvascular diabetic complications, regardless of proband renal status.

A multiple logistic regression analysis was performed with DN (micro- and macroalbuminuria and ESRD) in the probands as the dependent variable, and age, fasting plasma glucose levels (per 5 mmol/l), diabetes duration of the probands (per 5 years), and presence of DN and diabetes duration of the sibling as independent variables (Table 4). The presence of proband DN was significantly associated with DN in the sibling (OR = 3.76, 95% CI = 1.36–10.40, P = 0.011), adjusted for the proband's fasting plasma glucose (OR = 5.04, 95% CI = 5.03–5.05, P = 0.012) and diabetes duration (OR = 5.4, 95% CI = 5.05–5.7, P = 0.046).

Figure 1 depicts the siblings' cumulative prevalence of DN during the years after diabetes diagnosis according to proband renal status. Prevalence of DN in the siblings increased with diabetes duration, and it was higher when the probands had DN. After 25 years of known diabetes duration, DN was detected in 57.5% of the siblings of the probands with DN, compared with 16.9% of the siblings of the probands without DN.

DISCUSSION

In the present study, it was observed that DN in probands was significantly associated with the presence of DN in the sibling, as well as with the proband's glucose levels and known duration of diabetes. This suggests that genetic predisposition and environmental factors are important determinants for the

TABLE 2
Clinical and laboratory characteristics of type 2 diabetic siblings grouped according to proband stage of DN

Sibling characteristics	Siblings of probands with			*P*
	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	
n	58	20	29	—
Sex (male)	53	40	37.9	0.091
Age (years)	57.5 ± 7.8 (38–74)	58.4 ± 11.1 (40–77)	55.3 ± 8.6 (34–74)	0.547
Diabetes duration (years)	9.91 ± 5.3 (5–28)	9.8 ± 5.2 (5–25)	9.25 ± 5.3 (5–25)	0.066
BMI (kg/m^2)	29.5 ± 5.9 (22–48)	27.5 ± 5.5 (20–37)	31.9 ± 5.6 (24–47)	0.067
Systolic blood pressure (mmHg)	157.3 ± 22.2 (102–200)	165.1 ± 14.1 (124–196)	159.0 ± 24.2 (106–200)	0.678
Diastolic blood pressure (mmHg)	97.4 ± 15.3 (70–120)	100.0 ± 15.0 (80–128)	100.3 ± 19.0 (70–124)	0.759
Hypertension	72.9	75.0	87.3	0.921
Antihypertensive treatment*	72.7	66.7	65.2	0.701
Retinopathy	31	45.0	41.4	0.516
Insulin use	12.1	20.0	10.3	0.580
GHb (%)	8.61 ± 2.5 (4.2–13.4)	8.48 ± 2.3 (4.6–12.0)	9.54 ± 2.8 (6.4–13.8)	0.460
Creatinine (μmol/l)	82.21 ± 13.26 (53.04–106.08)	83.98 ± 19.45 (44.2–123.76)	76.02 ± 8.84 (53.4–99.01)	0.532
UAER‡ (μg/min)	15.3 (1–863)	64.6 (2.9–1,873.0)	850.36 (0.55–1,000)	0.011†

Data are %, means ± SD (range), or median (range). *P* values are by χ^2 or ANOVA. *All antihypertensive agents included. †Normo- vs. micro- vs. macroalbuminuric groups.

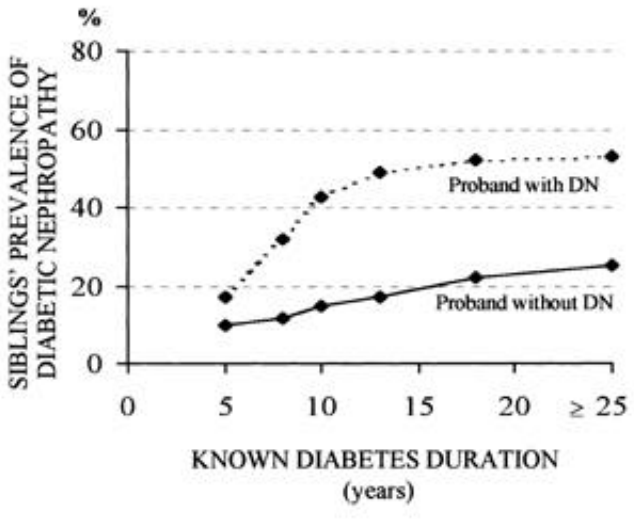

FIG. 1. Prevalence of DN in the siblings according to proband renal status.

development of DN. Studies suggest that familial aggregation of environmental factors alone cannot explain the familial aggregation of diseases (17). Even when subjects are exposed to a strong environmental risk factor, the familial clustering of diseases can only be explained by the presence of genetic susceptibility (17,18).

It is well known that the proportion of DN in type 1 diabetic patients increases with duration of the disease, reaching a plateau ~15 years after puberty (19). This is less clear in type 2 diabetic patients, and a significant proportion of these patients already present some chronic complications at the time of diabetes diagnosis (20). In fact, the diagnosis of diabetes in type 2 diabetic patients is made 4–7 years after the onset of hyperglycemia (21). In some of our normoalbuminuric patients, diabetes had not been present for sufficient time to guarantee that they would not develop DN in the future. However, the mean known diabetes duration of normoalbuminuric siblings of normo-, micro-, or macroalbuminuric probands was similar (~7 years). Longer diabetes duration would increase the proportion of DN in the three groups in a similar fashion and would not decrease the magnitude of the effect of genetic susceptibility. Furthermore, when we analyzed the familial clustering by taking into account only the patients with known diabetes duration >10 years, we still found a significant association (P = 0.012).

The OR of 3.24 for DN in siblings whose proband had micro- or macroalbuminuria or ESRD was similar to the values of 3.94, 4.9, and 2.5 reported by other authors for Caucasian type 2 diabetic patients (10) and for type 1 diabetic patients (2,3). Yet another study observed an OR of 24 for type 1 patients, but that study included only normoalbuminuric subjects and patients with advanced renal disease (recipients of a renal transplant) (1). The observation of a very similar risk in groups of patients from different genetic backgrounds suggests that familial clustering of DN is a consistent finding in type 1 and type 2 diabetic patients. It is interesting to note that this similarity occurred in spite of the difference in criteria used by the authors to establish the presence of DN. Faronato et al. (10) observed a familial clustering of DN in a sample of type 2 diabetic patients composed mainly (83%) of microalbuminuric probands (UAER ≥30 μg/min). In our study, the microalbuminuric probands represented 44% of the DN in the proband group, and when analyzing the familial aggregation of microalbuminuria alone (normo- vs. microalbuminuric patients), we were unable to find an association. This could be due to the smaller number of microalbuminuric probands in our study (n = 18, power = 25%). On the other hand, considering only patients in advanced stages of DN (macroalbuminuria and ESRD), the calculated OR (OR = 7.72) was higher than the observed OR when microalbuminuric patients were included in the DN group (OR = 3.24).

The ethnic distribution of the sample of diabetic patients is representative of the population of our state. All the patients evaluated were living in Rio Grande do Sul, the southernmost state of Brazil, where 86% of the population consists of white people of European origin, with African and Latin-American

TABLE 3
Nephropathy status of type 2 diabetic siblings according to proband renal status

Proband renal status*	n*	Sibling renal status			Sibling total
		Normoalbuminuric	Microalbuminuric	Macroalbuminuric	
n†	—	66	28	13	107
Normoalbuminuric	49	43 (74.1)	12 (20.7)	3 (5.2)	58 (100)
Microalbuminuric	18	10 (50)	7 (35.0)	3 (15.0)	20 (100)
Macroalbuminuric	23	13 (44.8)	9 (31.0)	7 (24.1)	29 (100)

Data are n (%). P = 0.024, Fisher's exact test. *Number of probands; †number of siblings.

TABLE 4
Multiple logistic regression analysis with DN (micro- and macroalbuminuria and ESRD) in the probands as the dependent variable

Variables	OR (95% CI)	P
DN in the sibling (absent/present)	3.76 (1.36–10.04)	0.011
Proband fasting plasma glucose (5 mmol/l)	5.04 (5.03–5.05)	0.012
Proband diabetes duration (5 years)	5.40 (5.05–5.75)	0.046

Proband age and sibling diabetes duration were excluded from the model.

ancestries less represented (13). The families included in the study reflect the state ethnic distribution, since the proportion of white families varied from 77.8 to 83.7% (Table 1). However, it is important to emphasize that in Brazil, most information regarding ethnic distribution relies on self-reporting of skin color. The ethnic categorization based on phenotype characteristics and on self-reporting of skin color is subjective and imprecise and could lead to misclassification (22–24).

The prevalence of DN among outpatients was similar to that reported in population-based studies (25,26). The characteristics of type 2 diabetic patients with micro- and macroalbuminuria and ESRD were similar to the characteristics of patients with DN described by other authors. The probands with DN were older and had a longer known diabetes duration and worse metabolic control than the normoalbuminuric probands. Almost 90% of the patients presented diabetic retinopathy.

The number of hypertensive normoalbuminuric probands was similar to the figures reported by other authors (27), but the proportion of hypertension in the group of macroalbuminuric probands was lower than expected (78 vs. 93%) (27). This can be explained by two facts. First, this group included patients with ESRD on dialysis, which may normalize the blood pressure in some patients. Secondly, patients with increased blood pressure have an increased mortality rate when compared with normotensive individuals, which could result in a reduced number of hypertensive patients. Although these two situations represent a limitation of cross-sectional studies, as is the case of the present work, we believe they did not have a significant impact on our conclusions.

Another potential limitation of this study is the possible systematic nonidentification of families with a less severe degree of diabetic complications. Actually, the number of families identified represented 58% of the expected number of eligible families. Because it is easier to identify sib pairs when both are affected by DN, there could be an ascertainment bias in favor of findings confirming familial clustering of DN. Although the renal status was not known during the ascertainment process, the study design does not prevent this type of selection problem. On the other hand, type 2 diabetic patients with nephropathy presented an increased mortality rate due mainly to cardiovascular disease (28), and, therefore, an undercounting of affected siblings could have occurred. This survival bias could also explain the lower than expected proportion of hypertension in macroalbuminuric probands. Although these biases have opposite effects and different magnitudes, they do not cancel each other; still, we believe that they were not important enough to compromise the results of the present study.

In conclusion, there is a familial aggregation of DN in this Brazilian sample of type 2 diabetic patients.

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