Increased Familial History of Arterial Hypertension, Coronary Heart Disease, and Renal Disease in Brazilian Type 2 Diabetic Patients With Diabetic Nephropathy

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OBJECTIVE — To evaluate whether there is a familial association of arterial hypertension, coronary heart disease, renal disease, and stroke with diabetic nephropathy.

RESEARCH DESIGN AND METHODS — There were 115 outpatients and 34 patients with end-stage renal disease treated by hemodialysis (61 men, age range 41–81 years) and having at least one sibling with type 2 diabetes studied. The positive or negative history of siblings (n = 765) was assessed by a standard questionnaire. The urinary albumin excretion rate (UAER) was measured by radioimmunoassay in 24-h sterile urine (three samples). The subjects were grouped as normoalbuminuric (UAER <20 μg/min, n = 59), microalbuminuric (UAER 20–200 μg/min, n = 35), macroalbuminuric (UAER >200 μg/min, n = 21), and end-stage renal disease (n = 34).

RESULTS — Patients with microalbuminuria, macroalbuminuria, or end-stage renal disease had an increased prevalence of sibling history of arterial hypertension (33.2, 37.3, and 33.8 vs. 23.4%, $P < 0.001$) and coronary heart disease (15.2, 17.0, and 19.4 vs. 10.2%, $P = 0.044$) compared with the normoalbuminuric group. The renal disease history was increased only in the siblings of patients with macroalbuminuria or end-stage renal disease (12.8 and 15.6 vs. 7.6 and 6.1%, $P = 0.005$). The presence of sibling arterial hypertension strongly increases the prevalence of sibling renal and coronary heart disease independent of patient renal status.

CONCLUSIONS — There is an association of diabetic nephropathy and sibling history of arterial hypertension and renal and coronary heart disease in type 2 diabetic patients. These associations are not independent, and arterial hypertension may be their main determining factor.

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Familial clustering of diabetic nephropathy (DN) has been demonstrated in type 1 diabetic patients (1–3), in Caucasians, and/or in selected groups of type 2 diabetic patients (4), suggesting a genetic predisposition to this diabetic complication. DN is classically associated with arterial hypertension and an increased prevalence of coronary heart disease (CHD). Although it is not known whether this association is only coincidental, there is evidence that increased levels of blood pressure (5) and/or abnormalities of blood pressure homeostasis (6) occur during the normoalbuminuric phase among subjects who progress to renal disease (RD). The association of arterial hypertension, CHD, and risk factors for CHD in nondiabetic parents of type 1 diabetic individuals with DN strongly supports the theory of a genetic predisposition to these diseases (7–10).

There are few data concerning the history of hypertension and RD in type 2 diabetic families, and all of them came from specific ethnic groups (11,12). The confirmation of this association in another population will reinforce the role of hypertension in the pathogenesis of DN.

The aim of this study was to analyze the familial clustering of cardiovascular disease, RD, and arterial hypertension in first-degree relatives of a group of type 2 diabetic patients in different stages of DN.

RESEARCH DESIGN AND METHODS

Subjects

Included in the study were all type 2 diabetic patients attending the outpatient clinic and all type 2 diabetic patients with end-stage renal disease (ESRD) treated in the dialysis unit of Hospital de Clínicas de Porto Alegre between March 1994 and March 1997 who had at least one sibling who also had type 2 diabetes. This criterion was used because this is part of another study carried out to analyze the familial clustering of DN. Hospital de Clínicas de Porto Alegre is a regional center, and the patients come from the whole state of Rio Grande do Sul, the southernmost state of Brazil. According to the latest demographic census (13), 86.7% of the population is classified as white, 8.4% as mulatto, 4% as black, and 0.9% as native, yellow, or not defined. The patient population of this center reflects this distribution. Type 2 diabetes was defined according to World Health

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Abbreviations: ANOVA, analysis of variance; CHD, coronary heart disease; DN, diabetic nephropathy; ESRD, end-stage renal disease; RD, renal disease; UAER, urinary albumin excretion rate.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Organization criteria: diagnosis of diabetes after the age of 30 years, no insulin treatment during the first 5 years after diagnosis, and absence of ketoacidosis episodes. Five male patients were excluded because they had cardiac failure, metastatic prostate cancer, persistent urinary tract infection after prostate surgery, hepatic cirrhosis, or alcoholism. A total of 115 diabetic outpatients and 34 patients in dialysis fulfilled these criteria. Each patient had a median of 4 siblings (1–14), with a total of 765 siblings. The protocol was approved by the Ethics Committee of the Hospital, and all patients gave their written informed consent to participate.

Patient evaluation

The patients answered a standard questionnaire and underwent physical examination and laboratory tests. They were weighed in light outdoor clothes without shoes, and height was recorded. BMI was calculated as weight (kilograms)/height (meters^2). Waist circumference was measured at the narrowest part, as viewed from the front, and the hip circumference at the widest part when viewed laterally, and the waist-to-hip ratio was calculated. Sitting blood pressure was measured twice on the right arm to the nearest 2 mmHg after a 10-min rest using a standard mercury sphygmomanometer (phases I and V of Korotkoff sounds). Hypertension was defined as blood pressure >140 mmHg and/or >90 mmHg or any value when antihypertensive drugs had been used. Fundus examination was performed by the ophthalmologist, after mydriasis. The findings were graded as follows: *1*) no signs of diabetic retinopathy; 2) nonproliferative retinopathy; or 3) proliferative retinopathy. The presence of CHD was evaluated by the World Health Organization questionnaire for cardiovascular disease (14) and 12-lead resting electrocardiogram (Minnesota Code: codes 1-3, 1-1, 1-2, 5-1, 5-2, 5-3, 7-1) (14). Glucose was measured by the glucose-oxidase method; GHb by electrophoresis (IMX, normal range: 5.3–7.5%, interassay coefficient of variation 6.5%); fructosamine by a colorimetric method (NBT reduction, Labtest; normal range: 1.87–2.87 mmol/l); creatinine by Jaffé's reaction; and cholesterol, HDL, and triglycerides by a colorimetric method. Urinary albumin was measured at least three times by radioimmunoassay (DPC, Los Angeles, CA; inter- and intra-assay coefficient of variation = 2.3 and 2.8%) in a 24-h timed sterile urine sample. The patients were grouped as normoalbuminuric (urinary albumin excretion rate [UAER] < 20 µg/min, n = 59), microalbuminuric (UAER 20–200 µg/min, n = 35), macroalbuminuric (UAER >200 µg/min, n = 21), and ESRD (dialysis, n = 34). Diabetic nephropathy was diagnosed in the outpatients by the presence of micro- or macroalbuminuria in two of three 24-h 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). In the dialysis group, the diagnosis of DN was assumed when proteinuria, hypertension, and retinopathy were present and there was no evidence of other RD.

Family history evaluation

The sibling history of hypertension, CHD, stroke, RD, and diabetes was taken from patients by a trained interviewer using a standard questionnaire. Initially, the names and ages of all patients' siblings, alive or deceased, were recorded. Thereafter, the following questions were asked to the patient: "Do you know if (your brother/sister's name) has or had cardiac disease, angina, heart attack, myocardial infarction?, kidney disease?, stroke?, hypertension or high blood pressure?". When the answer to one of these questions was "yes," the medications in use (or which had been used) and the physician's name and specialty or clinic were also asked. A CHD history was considered positive when the patient reported a history of a sibling with myocardial infarction, angina, or sudden death. The family history of RD was ascertained by reference to decreased renal function, dialysis, or renal treatment in a specialized clinic. Arterial hypertension histories were considered to be positive by previous diagnosis or by the use of specific antihypertensive medications. Stroke was defined by a previous diagnosis or history of compatible sequels. A negative or unknown answer was considered to be a negative history for statistical analysis. Only the history of siblings aged 30 years or older was included in the analysis.

The accuracy of information collected by the questionnaire (sibling history of hypertension, RD, CHD, and stroke) was ascertained by comparing it with data collected from 94 randomly selected siblings. These siblings underwent a complete clinical and laboratory evaluation. The presence of hypertension and CHD were established as described for the proband. RD was considered to be positive by the presence of microalbuminuria, macroalbuminuria, or impaired renal function (creatinine levels >1.5 mg/dl or ESRD). Stroke was confirmed according to compatible history and the presence of sequelae.

Statistical analysis

The prevalence of hypertension, stroke, RD, and CHD in siblings was described according to the patient's renal status and compared using the chi-square or Fisher's exact test. The continuous data are reported as means ± SD or median (range). Comparisons between groups were performed by one-way analysis of variance (ANOVA) or the Kruskal-Wallis test. The differences between groups were assessed by residual analysis or by the Tukey test (categoric and continuous data, respectively). A P value (two-sided) <0.05 was considered significant. To evaluate the possible independence of the sibling histories of hypertension, CHD, stroke, and diabetes and the patient's renal status, logistic regression analysis was performed using the step-wise forward approach. The proband renal status (normoalbuminuric versus microalbuminuric, macroalbuminuric, and dialysis) was entered as the dependent variable, and the proportion of affected siblings with hypertension, CHD, RD, diabetes, and stroke were included in the analysis as the independent variables. A P value of 0.10 was considered significant. All calculations were performed using the STATA and the SPSS statistical packages.

RESULTS

Patient and sibling data

The clinical and laboratory characteristics of diabetic patients are reported in Tables 1 and 2. The four groups were well matched for age and sex. Systolic and diastolic blood pressure levels were similar among the groups, but hypertension (defined by pressure levels and medicine use) was more prevalent in the DN groups. The groups of dialysis and macroalbuminuric patients had a longer duration of diabetes than did the normo- and microalbuminuric patients. Dialysis patients had a lower BMI when compared with the normo- and macroalbuminuric groups but presented a higher waist-to-hip ratio than all other groups. The prevalence of CHD and retinopathy was greater in the macroalbuminuric and the dialysis groups. Plasma glucose, GHb, fructosamine, cholesterol, and triglyceride levels were similar in all groups. As

Table 1—*Clinical characteristics of type 2 diabetic patients grouped according to stage of diabetic nephropathy*

	Normoalbuminuric	Microalbuminuric	Macroalbuminuric	Dialysis	*P*
n	59	35	21	34	
Sex (M/F)	18/41	18/17	8/13	17/17	0.145
Age (years)	57.3 ± 8.3 (42–76)	59.2 ± 9.6 (41–81)	61.0 ± 9.7 (45–81)	59.6 ± 10.4 (43–80)	0.161
Diabetes duration (years)	12.8 ± 6.3 (5–30)	13.0 ± 7.3 (5–30)	17.3 ± 8.0 (5–40)	18.0 ± 8.3 (5–45)	<0.001*
BMI (kg/m²)	28.4 ± 4.9 (18–42)	27.6 ± 3.7 (20–35)	29.9 ± 4.7 (23–42)	24.7 ± 3.5 (19–31)	<0.001†
Waist-to-hip ratio	0.91 ± 0.07 (0.80–1.10)	0.93 ± 0.08 (0.80–1.10)	0.93 ± 0.06 (0.8–1.02)	1.05 ± 0.16 (0.80–1.27)	<0.001‡
Systolic blood pressure (mmHg)	156 ± 27.9 (92–230)	160 ± 28.4 (100–240)	162 ± 23.3 (110–210)	158 ± 26.2 (100–200)	0.747
Diastolic blood pressure (mmHg)	96 ± 17.1 (60–150)	96 ± 20.5 (68–160)	95 ± 19.0 (60–140)	88 ± 13.8 (50–100)	0.180
Hypertension (positive/negative)	36/23	17/18	18/3	30/4	<0.01
CHD (positive/negative)	13/46	6/29	7/14	16/18	0.024
Retinopathy (no/nonproliferative/ proliferative)	36/18/5	9/20/6	4/10/7	0/4/30	<0.01

Data are means ± SD or number of cases with the characteristic analyzed (range). *P* was determined by χ^2 or ANOVA. *The macroalbuminuric and dialysis groups differ from the normo- and microalbuminuric groups (Tukey test). †The dialysis group differs from the normo- and macroalbuminuric groups (Tukey test). ‡The dialysis group differs from all other groups (Tukey test).

expected, serum creatinine levels were higher in the dialysis group.

The sibling group was formed by 765 individuals, and their clinical characteristics are shown in Table 3. The siblings of probands with normo-, micro-, and macroalbuminuria and dialysis did not differ regarding age, proportion of men, and proportion of known diabetes.

Family history

The questionnaire provided information concordant with the clinical evaluation in 96.8% (91/94) of the cases for stroke, 83.0% (78/94) for RD, 80.9% (76/94) for CHD, and 71.3% (67/94) for hypertension. Twenty-seven cases were discordant for hypertension. Of the discordant cases, 4 were reported as being positive when they were negative; 13 were reported to be negative but were hypertensive; and 10 of the unknown cases had hypertension. The proportion of concordant/discordant cases did not differ among the siblings of probands with normoalbuminuria (69%), microalbuminuria (68%), macroalbuminuria (72%), and dialysis (70%).

The data referring to the history of arterial hypertension, CHD, RD, and stroke in siblings of type 2 diabetic patients at different stages of DN are listed in Table 4. The prevalence of a history of increased blood pressure and CHD was higher in siblings of diabetic patients with micro- or macroalbuminuria or in dialysis than in the siblings of diabetic patients without DN. The siblings of macroalbuminuric or dialysis patients had a more frequent history of RD than did the siblings of patients with normo- or microalbuminuria. The history of stroke did not differ among groups.

When the prevalence of hypertension, RD, and CHD in the siblings according to the presence of a history of diabetes was analyzed (Fig. 1), it was observed that hypertension is more frequent in diabetic siblings ($P < 0.001$) and increases in both diabetic and nondiabetic siblings of the probands with DN ($P < 0.05$). The prevalence of a history of RD was also higher in the diabetic siblings compared with the nondiabetic siblings ($P < 0.001$), and it was higher in those siblings of probands with micro- or macroalbuminuria or in dialysis than in the siblings of normoalbuminuric probands ($P < 0.05$). A history of CHD was more frequent in diabetic siblings of probands with DN, but this did not reach the chosen significance level ($P = 0.06$), probably because of a relatively lower frequency of CHD in siblings of macroalbuminuric probands.

The prevalence of CHD was higher in siblings with a history of hypertension than in those without a history of hypertension (30 vs. 4%; 34 vs. 6%; 34 vs. 7%; 39 vs. 10%; $P < 0.001$). This finding was independent of the probands' renal status (Fig. 2). A positive history of hypertension in siblings also increased the prevalence of RD in the siblings of diabetic probands with macroalbuminuria or in dialysis compared with the siblings of normo- and microalbuminuric probands (30 and 33% vs. 16 and 17%; $P < 0.05$) (Fig. 2).

Table 2—*Laboratory features of type 2 diabetic patients grouped according to stage of diabetic nephropathy*

	Normoalbuminuric	Microalbuminuric	Macroalbuminuric	Dialysis	*P*
n	59	35	21	34	
Blood glucose (mg/dl)	180.3 ± 77.7 (64–350)	190.3 ± 96.9 (55–350)	170.3 ± 79.0 (110–338)	190.9 ± 101.9 (110–396)	0.484
GHb (%)	7.13 ± 2.15 (2.7–11.6)	8.95 ± 2.09 (5.9–11.8)	7.76 ± 1.26 (6.3–9.3)	8.05 ± 1.48 (7.0–9.1)	0.148
Fructosamine (mmol/l)	3.84 ± 0.91 (2.27–6.62)	3.90 ± 0.89 (2.74–5.84)	3.74 ± 1.12 (1.01–5.33)	3.29 ± 1.11 (2.60–5.24)	0.584
Cholesterol (mg/dl)	217.7 ± 49.2 (85–321)	220.7 ± 46.6 (134–328)	223.3 ± 56.6 (120–342)	242.0 ± 33.6 (192–264)	0.806
Triglycerides (mg/dl)	174 (53–754)	142 (60–1236)	177 (67–431)	309 (230–407)	0.731
Creatinine (mg/dl)	0.89 ± 0.20 (0.6–1.3)	0.93 ± 0.26 (0.5–1.6)	1.49 ± 1.20 (0.6–6.0)	12.81 ± 3.01 (7.0–17.4)	<0.001*
UAER (μg/min)	6.58 (0.76–19.0)	46.82 (21.0–187.57)	626.64 (202.45–2400)	—	—

Data are means ± SD or median (range). *P* was determined by ANOVA. *The dialysis group differs from all other groups (Tukey test).

Table 3—*Clinical characteristics of the siblings of type 2 diabetic patients grouped according to stage of diabetic nephropathy*

Siblings' characteristics	Patients' renal status				All siblings	*P*
	Normoalbuminuric	Microalbuminuric	Macroalbuminuric	Dialysis		
n	59	35	21	34		
Age (years)	52.3 ± 12	56.6 ± 18	54.8 ± 20	52.3 ± 16	54.4 ± 18	0.693
Sex (M/F)	126/169 (42.8)	97/100 (49.2)	48/70 (40.7)	74/81 (47.7)	345/420 (45.1)	0.305
Known diabetes	104/191 (35.3)	71/126 (36)	47/71 (39.8)	44/111 (28.4)	266/499 (34.8)	0.232
Total siblings	295	197	118	155	765	—

Data are means ± SD or positive/negative history (percentage of positive cases). *P* was determined by χ^2 test.

To evaluate the association of sibling history of hypertension, RD, CHD, stroke, and diabetes with probands' renal status, a multiple logistic regression analysis was performed. The history of sibling hypertension emerged as the only variable significantly associated to probands' RD ($\beta = 0.0128$; SE = 0.0062; $R = 0.1137$; $P = 0.038$).

CONCLUSIONS — An association of hypertension, cardiovascular disease, and DN was observed in type 2 diabetic patients' families. Our results suggest that hypertension plays a central role in the association of cardiovascular diseases and DN in type 2 diabetic patients. In type 1 diabetic patients, other authors demonstrated that the presence of hypertension (7,8), cardiovascular disease (9), and cardiovascular risk factors (10) in parents are associated with the development of DN in diabetic offspring. Blood pressure abnormalities were recently described in normotensive, normoalbuminuric type 1 diabetic patients with glomerular hyperfiltration (15), which is considered a risk factor for DN by some authors (16). This line of evidence suggests that genetic predisposition to hypertension/cardiovascular disease and early abnormalities of blood pressure homeostasis may predispose diabetic patients to RD.

There are very few studies on type 2 diabetic patients, and they were performed on selected groups, such as Native-American and Japanese patients. Takeda et al. (12) demonstrated in a Japanese population that the father and sibling history of hypertension was associated with the presence of proteinuria in type 2 diabetic patients. In Pima Indians with type 2 diabetes, the presence of measured hypertension in both parents was associated with an increased prevalence of proteinuria in the offspring (17). The population of the state of Rio Grande do Sul is mainly composed of white people of European origin, and people of African and Latin-American ancestry are less represented. However, some genetic heterogeneity is expected due to mixing between people of different origins. It is very difficult to characterize the ethnic aspect of a population based on phenotype characteristics such as self-reported skin color. This issue has been recently raised in the medical literature (18–20). The authors concluded that it is a subjective and imprecise method (18,20) and may give rise to misclassification depending on where the research takes place: "What is black to someone from the United States, for example, may be white to a Brazilian or a Caribbean islander" (20). In the present study, we confirmed and expanded the observation that an increased familial history of hypertension and cardiovascular disease is associated with DN in this population. This observation reinforces the hypothesis that atherosclerosis and glomerulosclerosis may share common genetic determinants (9,21).

This study was based on information collected during interviews with the proband. These data could be less accurate than the direct evaluation of the sibling regarding the presence of hypertension, CHD, RD, or stroke. However, this approach has been used successfully in previous studies (9,22). The presence of hypertension was discordant in ~30% of the siblings checked. A similar discordance rate (25%) was reported recently (22). In our study, the discordance was essentially related to the underreporting of hypertension by the proband. In 85% of the discordant cases, the proband reported no existence of hypertension in the sibling, when it was detected by direct evaluation. Furthermore, the discordance rate for the presence of hypertension was evenly distributed among the groups. Therefore, this fact did not seem to have influenced our results. Regarding the history of RD and CHD, the concordance was much greater.

Table 4—*Prevalence of history of arterial hypertension, coronary heart disease, renal disease, diabetes, and stroke in siblings of type 2 diabetic patients grouped according to stage of diabetic nephropathy*

Siblings' histories	Patients' renal status				All siblings	*P*
	Normoalbuminuric	Microalbuminuric	Macroalbuminuric	Dialysis		
n	59	35	21	34		
Hypertension	69/226 (23.4)	65/132 (33.0)	44/74 (37.3)	52/10 3 (33.5)	230/535 (30.1)	< 0.001†
CHD	30/265 (10.2)	30/167 (15.2)	20/98 (17.0)	30/125 (19.4)	110/655 (14.4)	0.044†
RD	18/277 (6.1)	15/182 (7.6)	15/103 (12.7)	24/131 (15.5)	72/693 (9.4)	0.005‡
Stroke	12/283 (4.1)	7/190 (3.6)	2/116 (1.7)	4/151 (2.6)	27/765 (3.3)	0.676
Total siblings	295	197	118	155	765	—

Data are number of siblings with positive/negative history (percentage of positive cases). *P* was determined by χ^2 or Fisher's exact test. *The normoalbuminuric group differs from all others. †The normo- and microalbuminuric groups differ from the macroalbuminuric and dialysis groups.

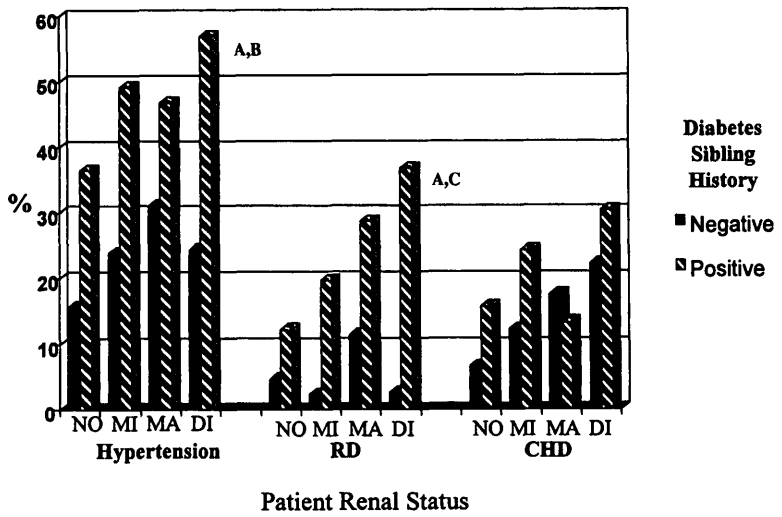

Figure 1—χ^2 *test. A: Diabetic siblings versus nondiabetic siblings (P < 0.001). B: Siblings of normoalbuminuric patients versus siblings of microalbuminuric, macroalbuminuric,and dialysis patients (P < 0.05). C: Siblings of normo- and microalbuminuric patients versus siblings of macroalbuminuric and dialysis patients (P < 0.05).*

However, we have to consider that the presence of RD may have been underestimated because microalbuminuria is not routinely screened by general practice physicians and does not determine alterations in routine kidney function tests.

Having at least one sibling with type 2 diabetes may have selected families prone to diabetes. The findings reported in this study may be limited to this type of family. However, our observation is not accounted for only by the increase in the prevalence of diabetic siblings, because the proportion of diabetic siblings was the same among groups. Furthermore, the increased history of hypertension in siblings of type 2 patients with DN still held true when we analyzed only the siblings without diabetes.

In conclusion, there is a familial association of hypertension, CHD, RD, and DN in type 2 diabetic patients. The association of these diseases is not independent, and hypertension could be the common link among them.

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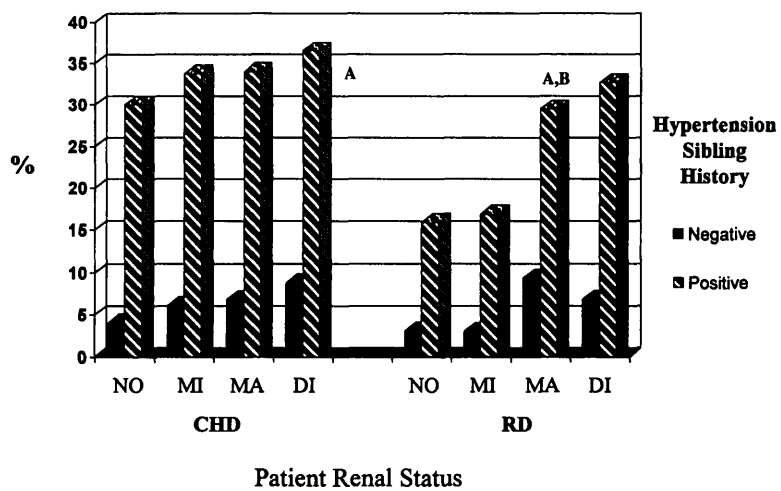

Figure 2—χ^2 *test. A: Hypertensive siblings versus normotensive siblings (P < 0.001). B: Siblings of normo- and microalbuminuric patients versus siblings of macroalbuminuric and dialysis patients (P < 0.05).*

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