

Predisposition to Essential Hypertension and Development of Diabetic Nephropathy in IDDM Patients

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Conflicting results have been reported on the relationship between familial predisposition to hypertension and development of diabetic nephropathy in IDDM. In our case-control study, we assessed the prevalence of hypertension among parents of 73 IDDM patients with diabetic nephropathy (DN⁺; persistent albuminuria >200 µg/min or >300 mg/24 h) and 73 IDDM patients without diabetic nephropathy (DN⁻; urinary albumin excretion <20 µg/min or <30 mg/24 h). Arterial hypertension, defined as antihypertensive therapy or a 24-h ambulatory blood pressure (SpaceLabs 90207)

135/85 mmHg, was present in 57% of parents of DN⁺ patients compared with 41% of parents of DN⁻ patients ($P = 0.034$; difference 16% [95% CI 1.3–29.6%]). In addition, the cumulative incidence of hypertension was higher among parents of DN⁺ patients (log-rank test $P < 0.001$), with a shift toward younger age at onset of hypertension in this group. However, the difference in prevalence of parental hypertension was not evident using office blood pressure measurements (64 vs. 57%; NS; difference 7% [-5.8–20%]). Furthermore, patients with DN⁺ and with antihypertensive therapy in both parents were themselves more frequently treated for hypertension than were patients with DN⁺ and without parental treatment for hypertension (100 vs. 61%; $P = 0.034$; difference 39% [21–57%]). In conclusion, familial predisposition to essential hypertension increases the risk of diabetic nephropathy and may also contribute to the development of systemic hypertension in patients with IDDM and diabetic nephropathy. *Diabetes* 47:439–444, 1998

Diabetic nephropathy occurs in roughly one-third of patients with IDDM (1–3). Prospective studies comparing the effects of conventional and intensive insulin therapy have demonstrated that improvement in glycemic control diminishes the risk of diabetic complications (4–6). Nevertheless, development of dia-

betic nephropathy cannot be explained by poor glycemic control alone (7). Because diabetic nephropathy has been found to cluster in families (8–10), it is reasonable to believe that diabetic nephropathy results from an interaction between genetic and environmental factors.

Diabetic nephropathy is characterized by persistent proteinuria, decline in renal function, increased cardiovascular morbidity and mortality, and, almost invariably, raised arterial blood pressure. Raised blood pressure in patients with diabetic nephropathy was considered to be a consequence of renal failure (11) until Viberti et al. (12) described elevated arterial blood pressure in parents of IDDM patients with proteinuria, which led them to propose that susceptibility to diabetic nephropathy is linked to genetic predisposition to hypertension. Results from an inception cohort from the Joslin Clinic supported this hypothesis: a parental history of hypertension was found to be more frequent in IDDM patients with diabetic nephropathy than in those without (13,14). However, the observation by Viberti et al. (12) was based on a single measurement of arterial blood pressure in a small number of parents. Subsequent larger studies have reported almost identical arterial blood pressure levels in parents of patients with and without diabetic nephropathy (15,16). Furthermore, several studies have found no significant excess of known hypertension in parents of patients with diabetic nephropathy (15–18). Consequently, the role of familial predisposition to essential hypertension in the development of diabetic nephropathy in IDDM has to be clearly defined. Therefore, our aim was to evaluate the association between predisposition to essential hypertension and diabetic nephropathy by recording previously known arterial hypertension, measuring office blood pressure, and monitoring 24-h ambulatory blood pressure, a method more sensitive than those previously used, in a large sample of parents of patients with and without diabetic nephropathy.

RESEARCH DESIGN AND METHODS

Thirty-seven IDDM patients with diabetic nephropathy (DN⁺) were consecutively selected, together with a control group of 38 IDDM patients with normal urinary albumin excretion rate (DN⁻) of comparable age, sex, and duration of diabetes (>15 years), from the outpatient clinic or the Dialysis Unit of Helsinki University Central Hospital in Helsinki, Finland (FIN). In addition, 94 cases from a random selection of all IDDM patients with diabetic nephropathy who had their glomerular filtration rate measured in 1993 and 90 patients from an age-, duration-, and sex-matched control group with normal urinary albumin excretion rate attending the outpatient clinic at the Steno Diabetes Center, Gentofte, Denmark (DK) (19) were included. Thus, a total of 131 patients with diabetic nephropathy and 128 patients with long-standing diabetes but without any signs of diabetic renal disease, all Caucasians, were included in the study.

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DK, Denmark; FIN, Finland.

TABLE 1
Clinical characteristics of IDDM patients and parents studied

	IDDM patients		Parents	
	DN ⁺	DN ⁻	DN ⁺	DN ⁻
<i>n</i>	73	73	109	112
Sex (M/F)	39/34	36/37	42/67	42/70
Country (FIN/DK)	29/44	29/44	44/65	45/67
Age (years)	37 ± 1	37 ± 1	66 ± 1	68 ± 1
BMI (kg/m ²)	24.8 ± 0.5*	23.7 ± 0.3	27.1 ± 0.5‡	25.9 ± 0.3
Smokers (%; 95% CI)	47 (35–59)	36 (25–47)	30 (22–39)	27 (19–35)
HbA _{1c} (%)	9.4 ± 0.2†	8.3 ± 0.1	6.2 ± 0.1	6.0 ± 0.1
Serum creatinine (μmol/l)	94 (57–1,141)†	78 (53–111)	85 (57–241)	86 (57–280)
Duration of diabetes (years)	25 ± 1	25 ± 1	—	—
Antihypertensive therapy (%; 95% CI)	75 (64–85)†	6 (1.5–13)	34 (25–43)§	20 (12–27)

Data are means ± SE or medians (ranges) unless otherwise stated. * $P = 0.043$, † $P < 0.001$ comparing patients with DN⁺ and patients with DN⁻; ‡ $P = 0.038$ and § $P = 0.016$ comparing parents of DN⁺ and parents of DN⁻.

All patients had been treated with insulin since diagnosis and were receiving at least two daily injections of insulin. Diabetic nephropathy was defined as an albuminuria exceeding either 200 μg/min (timed overnight urine collections, FIN) or 300 mg/24 h (24-h urine collections, DK) in two out of three consecutive collections; presence of retinopathy; and absence of any clinical or laboratory evidence of other kidney or renal tract disease. All subjects without nephropathy had a urinary albumin excretion rate persistently below 20 μg/min (FIN) or 30 mg/24 h (DK). Giving their informed consent to participate in the study were 123 DN⁺ patients and 124 DN⁻ patients. Of the possible 246 parents of DN⁺ and 248 parents of DN⁻, we were not able to trace 10 parents of DN⁺ and 5 parents of DN⁻. Eighty-six parents of DN⁺ were dead compared with 101 parents of DN⁻ (NS), and 38 parents of DN⁺ and 28 parents of DN⁻ were unwilling or unable to participate. Five parents reported antihypertensive medication due to renal disease; three parents of patients with DN⁺ had themselves a diagnosis of diabetic nephropathy verified by a urinary excretion rate exceeding 200 μg/min in a timed overnight urine sample; one parent of a patient with DN⁻ had chronic glomerulonephritis; and one parent of a patient with DN⁻ received dialysis treatment due to polycystic kidney disease. These five parents were excluded from further analysis. Consequently, we were able to study 109 parents of 73 patients with DN⁺ and 112 parents of 73 patients with DN⁻ (see Table 1 for characteristics).

All participating parents gave their informed consent, and the local ethics committees approved the protocol. Body weight and height were measured, and BMI was calculated as weight/height² (kg/m²). A careful medical history regarding hypertension, diabetes, cardiovascular disease, smoking habits, and regular medication was taken from all participating parents using a modified World Health Organization questionnaire. Cardiovascular disease was defined as a history of acute myocardial infarction or stroke. IDDM in parents was defined as diabetes with onset before the age of 40 and treatment with insulin alone since diagnosis; other cases of diabetes were classified as NIDDM. Corresponding data on nonattending parents (deceased or unwilling/unable to participate) were given by the participating spouses. Smokers were defined as subjects smoking at least one cigarette, cigar, or pipe per day; all others were considered nonsmokers.

Essential hypertension in parents was defined as current use of antihypertensive medication, a 24-h ambulatory blood pressure exceeding or equal to 135/85 mmHg (20,21), or an office blood pressure exceeding or equal to 140/90 mmHg in the absence of any known cause of secondary hypertension. Of the 162 parents without antihypertensive medication, an office blood pressure was measured in all subjects, and 131 (81%) volunteered for a 24-h ambulatory blood pressure monitoring. The 31 parents (14 of DN⁺ and 17 of DN⁻) in whom a 24-h ambulatory blood pressure monitoring was not performed were slightly older (69 vs. 66 years; $P = 0.034$) but did not differ regarding sex, BMI, or office blood pressure.

Office blood pressure (mean value of three measurements) was measured auscultatorily (Korotkoff I-V) on the right arm with a Hawksley random zero sphygmomanometer (DK) or an ordinary calibrated mercury sphygmomanometer (FIN) using a properly sized cuff with the subject in sitting position after 5 min of rest. The 24-h ambulatory blood pressure was measured oscillometrically with a SpaceLabs 90207 device (SpaceLabs, Redmond, WA) (22). The monitor was checked before, after, and once monthly during the study by comparison to a calibrated mercury sphygmomanometer according to the instructions of the manufacturer. Two sizes of cuffs were used (24–32 cm and 32–42 cm) depending on the circumference of the upper arm. Subjects were instructed to hold their arm immobile at the time of the measurements and to

keep a diary of the time they went to bed and rose in the morning, but otherwise to maintain their normal daily activities. Blood pressure was measured every 15 min from 0700 to 2200 and every 30 min from 2200 to 0700. A blood pressure monitoring was accepted if there was at least one successful blood pressure recording per hour during at least 20 of the 24 h of monitoring. Three subjects did not fulfill these criteria and were excluded. In the remaining 128 subjects, blood pressure was obtained successfully in 95% of planned measurements. No editing was performed in recorded blood pressure measurements. A mean value for systolic and diastolic blood pressures was calculated for every hour. Daytime and nighttime blood pressures were calculated according to individually recorded awake and sleeping hours.

Assays. Urine albumin concentration was determined by radioimmunoassay (FIN; Albumin-RIA, Pharmacia, Uppsala, Sweden) or enzyme immunoassay (DK) (23). Glycosylated hemoglobin was determined by high-pressure liquid chromatography (normal range 4.0–6.0% [FIN] and 4.1–6.1% [DK]). Serum creatinine was measured by a kinetic Jaffé method (normal range: women 50–110, men 55–115 μmol/l [FIN]; women 40–110, men 60–130 μmol/l [DK]).

Statistical analysis. The significance of the difference in categorical variables was tested with the χ^2 test. The significance of the difference in continuous variables was tested using analysis of variance (normally distributed) with and without age and BMI as covariates, or the Mann-Whitney U test (non-normally distributed). The cumulative incidence of hypertension in parents was calculated for 1-year intervals with a life-table method, which takes into account the variability in length of follow-up. Parents contributed person-years to follow-up until onset of hypertension, defined as either total hypertension (age when antihypertensive therapy was instituted or when 24-h ambulatory blood pressure $\geq 135/85$ mmHg) or treated hypertension (age when antihypertensive therapy was instituted). Those who remained normotensive contributed person-years to follow-up to the age at the time of the study. The significance of the difference in cumulative incidence between the two groups was determined using the log-rank test. All statistical analysis was performed on commercially available software (95% CIs were calculated using Confidence Interval Analysis version 1.0, and all other analysis was performed on a STATISTICA 4.1 statistical package). A two-tailed P value < 0.05 was considered statistically significant.

RESULTS

Antihypertensive therapy due to essential hypertension was present in 34% (37/109) of parents of DN⁺ and in 20% (22/112) of parents of DN⁻ ($P = 0.016$; difference between proportions 14% [95% CI 2.8–26%]). The 24-h ambulatory blood pressure measured in 128 (55 of DN⁺ and 73 of DN⁻) of the 162 parents without antihypertensive medication did not differ between the two groups of parents (Fig. 1, Table 2). However, the total number of parents with hypertension (antihypertensive medication or a 24-h ambulatory blood pressure exceeding or equal to 135/85) was 57% ($n = 52/92$) among parents of DN⁺ compared with 41% (39/95) among parents of DN⁻ ($P = 0.034$; difference 16% [1.3–29.6%]).

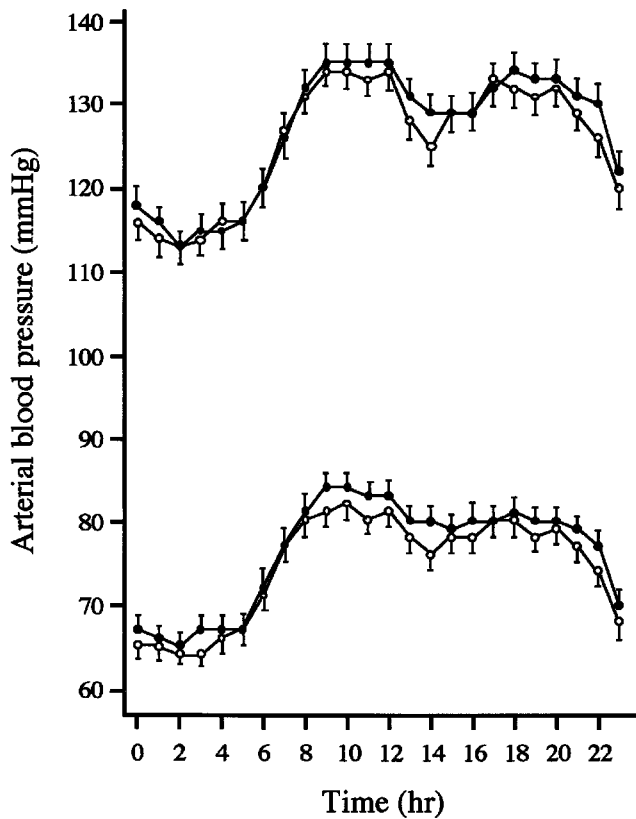


FIG. 1. Twenty-four-hour systolic (upper curves) and diastolic (lower curves) ambulatory blood pressure profiles in parents of DN⁺ (●) and parents of DN⁻ (○) without antihypertensive medication. Data are means \pm SE. There were no significant differences in systolic or diastolic blood pressure between the two groups.

Office blood pressure was measured in all 162 parents without antihypertensive medication (Table 2). No difference in office blood pressure between the two groups of parents without antihypertensive medication was found. The overall prevalence of hypertension (defined as antihypertensive medication or an office blood pressure exceeding or equal to 140/90) did not differ between parents of DN⁺ and parents of DN⁻ (64% [$n = 70/109$] vs. 57% [$n = 64/112$]; NS, difference 7% [-5.8–20%]). In the subset of parents with antihypertensive medication or with an ambulatory blood pressure monitoring performed, the prevalence of hypertension based on office blood pressure measurements was 67% ($n = 62/92$) in parents of DN⁺ and 55% ($n = 52/95$) in parents of DN⁻ (NS, difference 12% [-1.2–26%]). The overall prevalence of hypertension assessed by office blood pressure measurements in the parents who did not volunteer for 24-h ambulatory monitoring was not different from the rest of the parents within the corresponding group (DN⁺ 8/17 vs. 62/92, NS; DN⁻ 12/17 vs. 52/95, NS). Comparison of the two methods used for classification of untreated hypertension revealed that of the subjects classified as hypertensive by office blood pressure measurements ($n = 55$), less than 50% ($n = 26$) were found to be persistently hypertensive when assessed by 24-h ambulatory blood pressure monitoring. On the other hand, a majority of subjects with a normal office blood pressure ($n = 73$) also had a 24-h ambulatory blood pressure in the normotensive range ($n = 67$).

TABLE 2

Office and ambulatory blood pressure in parents without antihypertensive medication

	Parents of DN ⁺	Parents of DN ⁻
Office blood pressure		
<i>n</i>	72	90
Systolic	141 \pm 2	142 \pm 2
Diastolic	83 \pm 1	82 \pm 1
Proportion 140/90 (%)	46	47
Ambulatory blood pressure		
<i>n</i>	55	73
24 h systolic	126 \pm 2	126 \pm 1
Daytime systolic	131 \pm 2	131 \pm 2
Nighttime systolic	116 \pm 2	115 \pm 2
24 h diastolic	76 \pm 1	74 \pm 1
Daytime diastolic	81 \pm 1	79 \pm 1
Nighttime diastolic	67 \pm 1	65 \pm 1
Proportion 135/85 (%)	27	23

Data are means \pm SE unless otherwise stated. There was no significant difference in any variable between parents of DN⁺ and parents of DN⁻.

The cumulative incidence of hypertension was higher in parents of DN⁺ than in parents of DN⁻, independent of whether hypertension was defined as total hypertension (Fig. 2A) or treated hypertension (Fig. 2B).

In 28 patients with DN⁺ and 30 patients with DN⁻, both parents were examined (Fig. 3). There were more patients with hypertension in both parents in the DN⁺ group. After the inclusion of data on nonattending parents given by participating spouses, absence or presence of antihypertensive medication could be determined in both parents of 63 patients with DN⁺ and 68 patients with DN⁻. There were more patients with DN⁺ with antihypertensive medication in one or both parents (56 vs. 29%; $P = 0.002$, difference 27% [9.8–42%]). In addition, among patients with DN⁺, parental antihypertensive therapy was associated with an increased risk of systemic hypertension in the patients themselves (Fig. 4). A similar analysis could not be performed on patients with DN⁻ because of the small number of subjects with hypertension.

Furthermore, we were able to get information on cardiovascular disease and diabetes in 141 parents of DN⁺ and 145 parents of DN⁻. Cardiovascular disease was reported in 29 parents of DN⁺ compared with 26 parents of DN⁻ (NS, difference 2.6% [-6.5–12%]). Diabetes was present in 22 (NIDDM 17, IDDM 5) parents of DN⁺ and in 11 (NIDDM 10, IDDM 1) parents of DN⁻ ($P = 0.034$, difference 8.0% [-0.6–15%]).

To evaluate the impact of potential confounding factors, the parents were stratified according to obesity and age. The prevalence of hypertension, defined as abnormal 24-h ambulatory blood pressure or antihypertensive therapy, in parents with a BMI above the median did not differ from parents with a BMI below the median (52 vs. 48%, NS), but it was higher in parents above the median age compared with parents below (59 vs. 41%, $P = 0.014$).

DISCUSSION

In the present study, we report an increased prevalence of hypertension, defined as antihypertensive medication or a 24-h

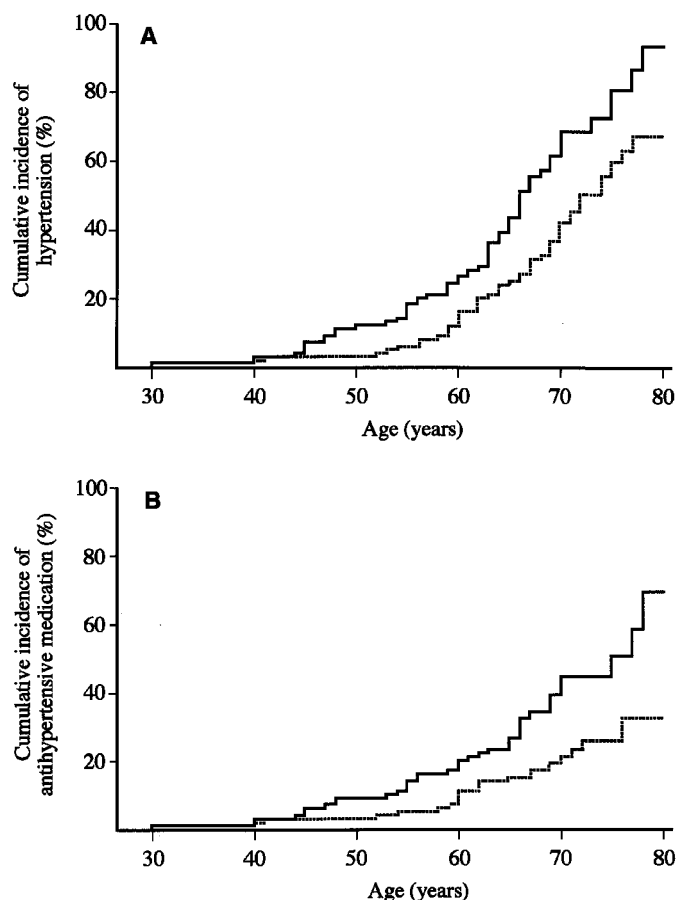


FIG. 2. A: Cumulative incidence of total hypertension (initiation of antihypertensive medication or age when 24-h ambulatory blood pressure monitoring $135/85$) in parents of DN⁺ (—; $n = 92$) and parents of DN⁻ (----; $n = 95$) patients. The cumulative incidence of hypertension was higher in parents of DN⁺ patients (log-rank test: $P < 0.001$). **B:** Cumulative incidence of initiation of antihypertensive medication in parents of DN⁺ (—; $n = 109$) and parents of DN⁻ (----; $n = 112$) patients. The cumulative incidence of antihypertensive medication was higher in parents of DN⁺ patients (log-rank test: $P = 0.002$).

ambulatory blood pressure monitoring in the hypertensive range, in parents of patients with diabetic nephropathy as compared with parents of patients without. The cumulative incidence of hypertension was higher among parents of patients with nephropathy, with a shift toward younger age at onset of hypertension. In addition to an association with development of diabetic renal disease, parental hypertension was also associated with development of arterial hypertension in patients with diabetic nephropathy.

We studied parents of IDDM patients with and without diabetic nephropathy regarding presence or absence of hypertension. To avoid misclassification of control subjects (future development of diabetic nephropathy), we included only patients with a long duration (mean 25 years) of IDDM. In their parents, the prevalence of antihypertensive medication due to essential hypertension was recorded. In parents without antihypertensive medication, office and 24-h ambulatory blood pressure was measured. Regardless of method used, no difference in blood pressure between the two groups of parents was found. However, there was an

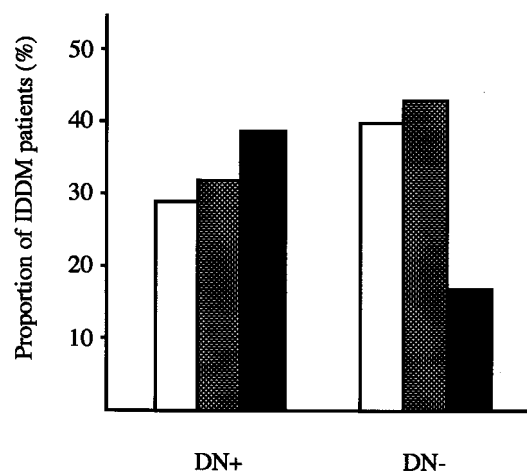


FIG. 3. Distribution of IDDM patients with hypertension in neither (□), one (▨), or both parents (■) according to presence (DN⁺; $n = 28$) or absence (DN⁻; $n = 30$) of diabetic nephropathy. Includes only patients with both parents examined. Hypertension is defined as antihypertensive medication or 24-h ambulatory blood pressure $135/85$. Hypertension in both parents was more frequent among patients with DN⁺ than among patients with DN⁻ (39 vs. 17%; difference 22% [95% CI 1.4–45%], $df = 1$, $P = 0.054$).

increased prevalence of total hypertension, defined as antihypertensive medication or a 24-h ambulatory blood pressure in the hypertensive range, in parents of patients with diabetic nephropathy. This excess of total hypertension was not due to the higher degree of obesity seen in this group, because hypertension was equally common above the median value of BMI as below. In fact, considering that parents of patients with nephropathy tended to be younger and the prevalence of hypertension increased with age, the true difference in prevalence could be even larger than demonstrated. The difference in prevalence of total hypertension failed to reach statistical significance when office blood pressure was used to identify parents with untreated hypertension.

The diabetic patients had a mean age of 35 years, which resulted in a relatively high death rate among their parents. Therefore, we were able to determine presence or absence of total hypertension in both parents in less than half of the diabetic patients. In this subgroup, hypertension was more often present in both parents among patients with diabetic nephropathy. However, a nonattending parent is equally capable of transmitting any genetic and/or environmental determinant related to hypertension; therefore, attention must be paid to parents dead or unable or unwilling to participate. There was no difference in overall parental mortality in the two groups of patients included in this study. Furthermore, data on antihypertensive medication in parents dead or unwilling to participate collected from participating spouses enabled us to get information on treatment of hypertension in both parents in a majority of studied patients (86 and 93%, respectively). In this additional analysis, a parental history of hypertension was substantially more prevalent in patients with diabetic nephropathy, indicating that our results in the studied parents seem to be valid for the whole study population.

The cumulative incidence of both total and treated

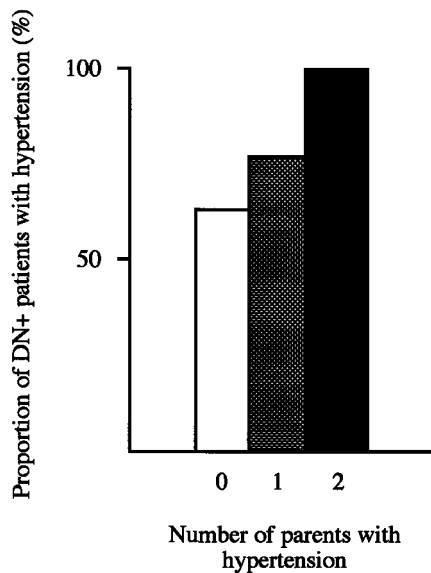


FIG. 4. Proportion of patients with DN⁺ treated with antihypertensive therapy according to antihypertensive therapy in neither (□; *n* = 28), one (▨; *n* = 27), or both (■; *n* = 8) parents. Includes only patients with data on antihypertensive treatment available for both parents. Patients with DN⁺ and with antihypertensive therapy in neither parent were themselves less frequently treated for hypertension than were patients with DN⁺ and with antihypertensive therapy in both parents (61 vs. 100%; difference 39% [95% CI 21–57%], *P* = 0.034).

hypertension was higher in parents of patients with diabetic nephropathy. Interestingly, hypertension was manifested at a younger age in this group of parents. The cumulative incidence curve started to rise around the age of 45 years in parents of patients with diabetic nephropathy, whereas the rise occurred approximately a decade later in parents of patients without nephropathy. After this initial difference in age at which hypertension was manifested, the cumulative incidence increased in an almost parallel manner in the two groups. This pattern could indicate that the excess of hypertension found in the parents of patients with diabetic nephropathy is mostly due to an excess of hypertension manifested at a relatively young age. The fact that the difference in prevalence of hypertension to a large extent was a consequence of more previously known hypertension among parents of patients with diabetic nephropathy (untreated hypertension was equally common in the two groups of parents) further supports this view. Therefore, there seems to be not only a quantitative but also a qualitative difference in parental hypertension between patients with and without diabetic nephropathy. This qualitative difference could possibly reflect a greater influence of genetic factors in the genesis of hypertension in the parents of patients with diabetic nephropathy that, when transmitted to the offspring with IDDM, increases susceptibility to diabetic renal disease.

In previous reports with data on parental hypertension in IDDM patients (12–18), there has been an overall tendency toward more hypertension in parents of patients with diabetic nephropathy. However, a statistically significant difference in blood pressure level (12) and in prevalence of hypertension (13,14) has been reported in only a minority of

published papers. There may be several reasons why the other studies (15–18) have not detected the excess of hypertension among parents of patients with diabetic nephropathy now confirmed by us. First, our study is the largest so far specifically aimed at addressing the question of a link between predisposition to hypertension and susceptibility to diabetic renal disease. Second, the control group in the present study has a longer duration of diabetes than any of the control groups of previous studies. Because the incidence of diabetic nephropathy decreases after the second decade of diabetes (1,2), a long duration will minimize the risk of future development of diabetic nephropathy and thereby the risk of misclassification. Third, our study demonstrates the well-known limitations of office blood pressure measured on a single occasion in identifying subjects with persistently elevated blood pressure.

The temporal relationship between the rise in arterial blood pressure and onset of abnormal albuminuria has been extensively studied in IDDM. Most (24–26) but not all (27) studies have found no difference in baseline arterial blood pressure in progressors from normo- to microalbuminuria compared with nonprogressors. However, as demonstrated in this study, once overt proteinuria is present, familial predisposition to hypertension seems to increase the risk of arterial hypertension. With respect to the indisputable relationship between elevated arterial blood pressure and accelerated loss of renal function (28), it is therefore likely that familial predisposition to hypertension may influence not only initiation but also progression of diabetic nephropathy.

Besides predisposition to hypertension, other suggested phenotypic markers for diabetic nephropathy are familial clustering of cardiovascular disease (17) and NIDDM (29,30). In the present study, the prevalence of self-reported cardiovascular disease (myocardial infarction or stroke) did not differ between parents of patients with and parents of patients without nephropathy. We have recently demonstrated a clustering of NIDDM in parents of IDDM patients with nephropathy after assessment of oral glucose tolerance (30). In the present study, we found more diabetes (IDDM and NIDDM combined) by medical history in parents of patients with nephropathy; NIDDM alone did not reach statistical significance, even if there was a tendency (*n* = 17 vs. *n* = 10). However, undiagnosed NIDDM is nearly as common as previously known NIDDM in elderly subjects (31). Medical history does not seem to be a sensitive-enough method to demonstrate a difference in the prevalence of parental NIDDM.

In conclusion, our results provide final support for a link between predisposition to essential hypertension and susceptibility to diabetic renal disease. In addition to an increased prevalence of hypertension in parents of patients with nephropathy, hypertension is manifested at a younger age, indicating qualitative differences in parental hypertension in IDDM patients with and without diabetic nephropathy. Furthermore, parental hypertension seems to increase the risk of arterial hypertension in offspring with IDDM and diabetic nephropathy.

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