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Parental hypertension and proteinuria in Pima Indians with NIDDM

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Summary To determine if parental hypertension is associated with proteinuria in offspring with non-insulin-dependent diabetes mellitus (NIDDM), 438 diabetic Pima Indians (172 men, 266 women) aged 20 years or more and both of their parents were examined. Hypertension was defined as a systolic blood pressure 140 mm Hg or more, diastolic blood pressure 90 mm Hg or more, or treatment with antihypertensive medicine. Sixty-three percent of the fathers and 80 % of the mothers had diabetes at the time their blood pressure was measured. Families in which either parent had proteinuria, defined as a urine protein-to-creatinine ratio ≥ 0.5 g/g were excluded; 73 (16.7 %) of the offspring had proteinuria. The prevalence rates of proteinuria in the offspring were similar if neither parent or only one parent had hypertension (8.9 and 9.4 %, respectively), but was significantly higher if both parents had hypertension (18.8 %), after adjustment for age, sex, duration of diabetes, and 2-h post-load plasma glucose concentration in the offspring and diabetes in the parents by logistic regression. The odds for proteinuria being present in the offspring if both parents had hypertension was 2.2 times (95 % confidence interval, 1.2 to 4.2) that if only one parent had hypertension. When mean arterial pressure and blood pressure treatment in the offspring were added to the model the relationship remained (odds ratio = 2.2; 95 % confidence interval, 1.1 to 4.3). Hypertension in both parents is associated with the development of proteinuria in offspring with NIDDM. This relationship was present even when controlled for the effects of blood pressure and its treatment in the offspring. [Diabetologia (1996) 39: 433–438]

Keywords Diabetic nephropathy, hypertension, familial predisposition, non-insulin-dependent diabetes mellitus, Pima Indians.

Genetic predisposition to hypertension has been proposed as a mechanism for the development of diabetic nephropathy in insulin-dependent diabetes mellitus (IDDM) [1–9]. This hypothesis is based in part on the observation that hypertension is more frequent and arterial blood pressure is higher in the parents [1–4] and siblings [5] of IDDM patients with proteinuria or microalbuminuria than in those without. Also it is based partly on the relationship between sodium-lithium countertransport activity in erythrocytes, a genetically influenced trait, and hypertension and renal disease in IDDM [2–3, 6–9].

Studies in Pima Indians suggest that both hypertension [10, 11] and familial factors [12] are associated with the development of renal disease in non-insulin-dependent diabetes mellitus (NIDDM). In the present study, we examine the relationship between parental hypertension and the development of nephropathy in Pima Indians with NIDDM.

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Abbreviations: IDDM, Insulin-dependent diabetes mellitus; JNC V, Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure; MAP, mean arterial pressure; NIDDM, non-insulin-dependent diabetes mellitus.

Subjects and methods

The Pima and closely-related Tohono O'odham Indians of the Gila River Indian Community of Arizona have participated in a study of diabetes and its complications since 1965. Each member of the community of 5 years of age or more is invited, regardless of health, to participate in a research examination every 2 years [13]. These biennial examinations include an oral glucose tolerance test with determination of the glucose concentration in venous plasma drawn after an overnight fast and 2 h after the ingestion of a 75-g carbohydrate load. World Health Organization criteria are used for the diagnosis of diabetes [14]. Blood pressure is measured to the nearest 2 mm Hg with a mercury sphygmomanometer while the subject rests in the supine position. Diastolic blood pressure is measured at the fourth Korotkoff sound. Hypertension was defined by Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V) criteria as a systolic pressure of 140 mm Hg or more, a diastolic pressure of 90 mm Hg or more, or treatment with antihypertensive medicine [15]. Mean arterial pressure (MAP) was calculated as the diastolic pressure plus one-third of the pulse pressure.

The presence of proteinuria is based on a single urine collection. Urine specimens collected at the end of the 2-h glucose tolerance test are examined for protein by dipstick and those containing at least a trace of protein are tested quantitatively for total protein by the Shevky-Stafford method [16]. Urine creatinine concentrations are measured with an autoanalyser and ratios of protein to creatinine (g protein/g creatinine) are calculated. Proteinuria was defined as a protein-to-creatinine ratio of 0.5 g/g or more, approximately equivalent to 0.5 g or more of protein in the urine each day [17–19].

Pima and Tohono O'odham Indian nuclear families with measurements of blood pressure, urine protein, and glucose tolerance in two successive generations were identified. Offspring 20 years of age or more who were at least 50 % Pima or Tohono O'odham Indian by heritage, for whom both parents had been examined when over 40 years of age, were eligible for inclusion in this analysis. The study was restricted to offspring who had NIDDM and whose parents were non-proteinuric.

Statistical analysis

Differences in mean age, duration of diabetes, 2-h post-load plasma glucose concentration and MAP in offspring according to the number of hypertensive parents were evaluated by analysis of variance. Differences in the prevalence of proteinuria and hypertension in offspring according to the number of hypertensive parents were evaluated by a Mantel-Haenszel chi-square test of general association. Differences in MAP among parents of offspring with proteinuria and those without were compared by a two-tailed *t*-test. The relationships between parental hypertension and proteinuria or hypertension in the offspring were evaluated by multiple logistic regression, which controlled for the effects of potentially confounding variables, selected because of their univariate associations with renal disease. The relationship between parental hypertension or diabetes and blood pressure (as a continuous variable) in the offspring was evaluated by multiple linear regression. There were no significant interaction terms in any of these analyses so such terms were not included in the final models. Two indicator variables were used for parental hypertension. The first indicator was given a value of "1" if either parent had hypertension and "0" if not and served as an indication of the effect of hypertension in one or both parents compared with neither parent having hypertension. The second indicator variable was assigned a value of "1" only if both parents had hypertension and "0" if not. This variable indicates the effect of both parents having hypertension compared with only one having hypertension. Odds ratios from the logistic models were calculated as described by Kleinbaum et al. [20]. Covariate-adjusted prevalence rates of proteinuria in the offspring were calculated from the regression models by covariance adjustment of rates to the mean values of the covariates in the sample [21]. Because observations within families are not independent of one another, an assumption of conventional regression techniques, the logistic regression analysis was also conducted using binomial generalized estimating equations, which allow for lack of independence among observations [22, 23].

Results

The study included 438 offspring from 219 fathers and 220 mothers. Of the 73 offspring with proteinuria, 34 (47 %) had one hypertensive parent and 30 (41 %) had two hypertensive parents. Of the 365 offspring without proteinuria, 191 (52 %) had one hypertensive parent and 82 (22 %) had two hypertensive parents. In only 101 of the 438 offspring did neither parent have hypertension. Average MAP (± SEM) in the parents of offspring with proteinuria (103 ± 1 mm Hg) tended to be higher than in those of offspring without proteinuria (99 ± 1 mm Hg, $p = 0.15$).

The prevalence of proteinuria in the offspring was 8.9 % if hypertension was present in neither parent, 15.1 % if it was present in one parent, and 26.8 % if it was present in both parents ($\chi^2 = 13.0$, $df = 2$, $p = 0.002$). On average, offspring with two hypertensive parents were older ($p < 0.001$), had diabetes of longer duration ($p < 0.001$), higher MAP ($p = 0.003$), and a greater frequency of hypertension ($\chi^2 = 9.9$, df = 2 $p = 0.007$) than the other groups. Table 1 shows the prevalence of proteinuria according to age, sex, duration of diabetes, blood pressure, and level of glycaemia. In most strata, the prevalence in offspring was higher if one or both parents had hypertension than if neither parent did.

Sixty-three percent of the fathers ($n = 138$) and 80 % of the mothers ($n = 176$) had diabetes at the time their blood pressure was measured. Figure 1 shows the prevalence of proteinuria in offspring according to parental diabetes and hypertension. The prevalence of proteinuria was higher in diabetic offspring whose mothers had diabetes than in those who did not, but the association was not significant when adjusted for age, sex, duration of diabetes and 2-h post-load plasma glucose concentration in the offspring by logistic regression (odds ratio = 2.4; 95 % confidence interval, 1.0 to 5.8). Diabetes in the father had little effect (odds ratio = 1.1; 95 % confidence interval, 0.6 to 1.9).

Parental hypertension was associated with proteinuria in the offspring, after adjustment for age,

Table 1. Number of offspring examined and prevalence (%) of proteinuria

Characteristics of offspring	Number of parents with hypertension					
	None		One		Two	
	n	Prevalence	*n*	Prevalence	*n*	Prevalence
Total	101	8.9	225	15.1	112	26.8
Sex						
Men	34	8.8	98	15.3	40	30.0
Women	67	9.0	127	15.0	72	25.0
Age (years)						
20–34	46	2.2	68	11.8	30	13.3
35–54	51	13.7	134	15.7	64	37.5
≥ 55	4	25.0	23	21.7	18	11.1
Duration of diabetes (years)						
< 5	68	2.9	87	8.1	42	11.9
5–9	11	0	51	9.8	21	9.5
10–14	9	33.3	44	15.9	23	17.4
≥ 15	13	30.8	43	34.9	26	73.1
Hypertension						
No	79	5.1	142	5.6	66	15.2
Yes	22	22.7	83	31.3	46	43.5
Mean arterial pressure (mm Hg)						
< 87	44	6.8	74	4.1	28	17.9
87–97	39	7.7	75	12.0	35	25.7
> 97	18	16.7	76	29.0	49	32.7
2-h plasma glucose (mmol/l)						
< 16.1	37	0	72	15.3	37	13.5
16.1–22.6	34	8.8	79	12.7	33	24.2
> 22.6	30	20.0	74	17.6	42	40.5

Prevalence of proteinuria according to age, duration of diabetes, hypertension, and tertiles of mean arterial pressure and plasma glucose concentration in the offspring and by the number of parents with hypertension

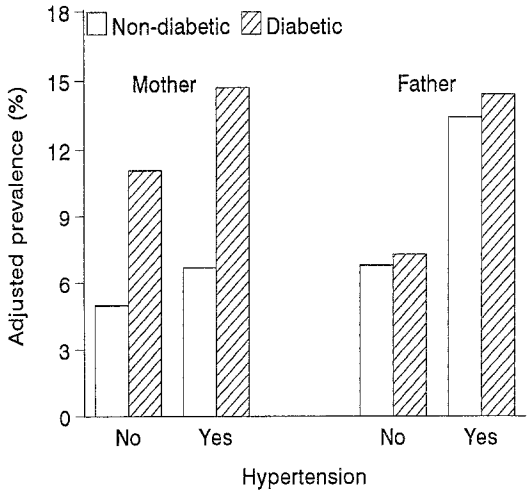

Fig. 1. Prevalence of proteinuria in offspring according to parental hypertension and NIDDM, adjusted for age, sex, duration of diabetes, and 2-h post-load plasma glucose concentration in the offspring

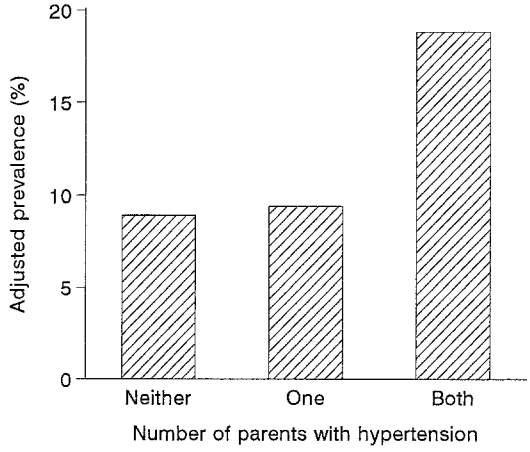

Fig. 2. Prevalence of proteinuria in offspring according to the number of parents with hypertension, adjusted for age, sex, duration of diabetes, and 2-h post-load plasma glucose concentration in the offspring

sex, duration of diabetes, and 2-h post-load plasma glucose concentration in the offspring and diabetes in the parents ($p = 0.03$, Table 2). Offspring with one hypertensive parent had a similar prevalence of proteinuria (9.4 %) to offspring of two normotensive parents (8.9 %, odds ratio = 1.1; 95 % confidence interval, 0.5 to 2.5), but the adjusted prevalence was significantly higher in the offspring with two hypertensive parents (18.8 %) than in those with only one hypertensive parent (odds ratio = 2.2; 95 % confidence interval, 1.2 to 4.2; Fig. 2). The relationship was similar when MAP and antihypertensive treatment in the offspring were added to the model (odds ratio = 2.2, 95 % confidence interval, 1.1 to 4.3), but the strength of the association was slightly reduced ($p = 0.05$, Table 2). Likewise, the point estimates from the generalized estimating equations were essentially unchanged from those obtained by conventional logistic regression (Table 2).

Parental hypertension was associated with blood pressure in the offspring ($p = 0.04$) when adjusted for age and sex of the offspring, but not when duration of diabetes and 2-h post-load plasma glucose concentration in the offspring and diabetes in the parents were added to the model ($p = 0.12$). When the relationship between parental hypertension and hypertension in the offspring was examined by logistic regression a modest, but not statistically significant association was found when adjusted for age and sex (odds ratio [hypertension in ≥ 1 parent/both parents normotensive] = 1.7; 95 % confidence interval, 1.0 to 3.0), and the relationship was weaker when duration of diabetes, and 2-h post-load plasma glucose concentration in the offspring and diabetes in the parents were added to the model (odds ratio = 1.6; 95 % confidence interval, 0.9 to 2.8). Parental diabetes was not associated with blood pressure in the offspring when adjusted for age and sex ($p = 0.12$), or when duration of diabetes and 2-h post-load plasma glucose concentration in the offspring were added to the model ($p = 0.15$).

Table 2. Odds ratios (and 95 % confidence intervals) of offspring having proteinuria according to various parental and offspring characteristics derived from conventional multiple logistic regression models and binomial generalized estimating equations, which allow for lack of independence among observations

Variable	Conventional logistic regression		Generalized estimating equations	
	Odds ratio[a]	95 % confidence interval	Odds ratio[a]	95 % confidence interval
Model A[b]				
HTN in at least one parent (0 = no, 1 = yes)	1.1	0.5–2.5	1.0	0.4–2.5
HTN in both parents (0 = no, 1 = yes)	2.2	1.2–4.2	2.1	1.0–4.4
Diabetes in mother (0 = no, 1 = yes)	2.4	1.0–5.8	2.3	0.9–5.9
Diabetes in father (0 = no, 1 = yes)	1.1	0.6–1.9	1.1	0.6–2.3
Age (per 5 years)	1.0	0.9–1.2	1.0	0.9–1.2
Sex (female = 0, male = 1)	1.6	0.9–2.8	1.4	0.8–2.4
Diabetes duration (per 5 years)	2.1	1.6–2.6	2.1	1.6–2.6
2-h plasma glucose (per 5 mmol/l)	1.2	1.0–1.6	1.2	1.0–1.4
Model B[c]				
HTN in at least one parent (0 = no, 1 = yes)	0.9	0.4–2.2	0.9	0.4–2.3
HTN in both parents (0 = no, 1 = yes)	2.2	1.1–4.3	2.2	1.0–4.6
Diabetes in mother (0 = no, 1 = yes)	2.4	0.9–6.0	2.3	0.9–6.0
Diabetes in father (0 = no, 1 = yes)	1.1	0.6–2.1	1.2	0.6–2.4
Age (per 5 years)	1.0	0.8–1.1	1.0	0.8–1.2
Sex (female = 0, male = 1)	1.1	0.6–2.2	1.1	0.6–2.0
Diabetes duration (per 5 years)	2.0	1.6–2.5	2.0	1.5–2.5
2-h plasma glucose (per 5 mmol/l)	1.2	1.0–1.7	1.2	1.0–1.4
Mean arterial pressure (per 10 mm Hg)	1.5	1.2–1.9	1.4	1.1–1.8
Antihypertensive treatment (0 = no, 1 = yes)	2.1	1.0–4.2	2.0	1.1–3.5

Age, sex, diabetes duration, blood pressure and glucose are offspring variables. Dependent variable: proteinuria in the offspring.

[a] Odds ratio for number of units shown in parentheses

[b] $p = 0.03$ for effect of parental HTN derived from comparing this model with the model omitting all terms involving parental HTN ($p = 0.09$ for the generalized estimating equation); $p = 0.12$ for effect of parental diabetes derived from comparing this model with the model omitting all terms involving parental diabetes ($p = 0.22$ for the generalized estimating equation)

[c] $p = 0.05$ for effect of parental HTN derived from comparing this model with the model omitting all terms involving parental HTN ($p = 0.12$ for the generalized estimating equation); $p = 0.14$ for effect of parental diabetes derived from comparing this model with the model omitting all terms involving parental diabetes ($p = 0.22$ for the generalized estimating equation); $p < 0.001$ for effect of blood pressure in the offspring derived from comparing this model with the model omitting all terms involving blood pressure in the offspring ($p < 0.001$ for the generalized estimating equation)

HTN, Hypertension by JNC V criteria [15]

Discussion

Determinants of proteinuria in the diabetic offspring examined in this analysis included diabetes duration, 2-h post-load plasma glucose concentration, and blood pressure in the offspring, and hypertension in both parents. Although the effect of maternal diabetes was not statistically significant, the prevalence of proteinuria was over twice as high in offspring whose mothers had diabetes as in those who did not. The relationship with parental hypertension is compatible with several studies in IDDM that found higher blood pressure or a greater prevalence of hypertension in the parents of patients with elevated protein excretion than in those without [1–4]. Unlike these studies, however, in the present study a statistically significant effect was found only if both parents had hypertension, after adjustment for the effects of parental diabetes and age, sex, duration of diabetes, 2-h post-load plasma glucose concentration, blood pressure, and antihypertensive treatment in the offspring.

Viberti and co-workers [1] have reported that the mean systolic and diastolic blood pressures were significantly higher in the parents of IDDM patients with proteinuria than in those without. Similarly, Krolewski and co-workers [2, 3] have found that having one parent with hypertension, determined by mailed questionnaire, tripled the risk of proteinuria in the offspring with IDDM. On the other hand, Jensen and co-workers [24] concluded that parental hypertension did not play a significant role in the development of renal disease in IDDM because blood pressure was nearly identical in the parents of IDDM patients with proteinuria (albuminuria > 300 mg/24 h) and those with normal urinary albumin excretion. Nevertheless, 55 % of their diabetic patients with nephropathy had at least one parent with hypertension, whereas only 34 % of their normoalbuminuric patients had a hypertensive parent [24, 25]. Moreover, their results may have been different had they accounted for treatment of blood pressure in the parents. A previous study of familial aggregation of diabetic renal disease in Pima Indians found that blood pressure in the diabetic parents was not related to renal disease in the offspring [12]. Likewise, in the present study the average MAP in parents of

offspring with proteinuria was not significantly higher than in those of offspring without proteinuria, but when the effect of parental hypertension was examined according to JNC V criteria, which include blood pressure treatment in the definition, a significant relationship with proteinuria in the diabetic offspring was found.

Familial aggregation of blood pressure has been widely reported [26–31], and may reflect the sharing of environmental factors within families or a genetic susceptibility to hypertension. The effect of parental hypertension on proteinuria in the offspring may be mediated through higher blood pressure in the offspring. A role for blood pressure in the development of diabetic nephropathy, as suggested in part by the results of the present analysis, has been proposed based on the relationship between higher blood pressure in diabetic Pima Indians and the development of proteinuria [10] and the relationship between higher *prediabetic* blood pressure and the development of proteinuria in Pima Indians after the onset of NIDDM [11]. In the present study, however, in keeping with a previous study in children from the Pima population [32], a significant association between parental hypertension and hypertension or blood pressure in the offspring was not found after controlling for parental diabetes. This finding suggests that the effect of parental hypertension on blood pressure in the offspring alone may not account completely for the enhanced susceptibility to renal disease seen among the diabetic offspring of two hypertensive parents.

Offspring whose parents had proteinuria, regardless of whether or not they had diabetes, were excluded from the present study to reduce the chance that parental hypertension due to kidney disease would obscure the relationship between essential hypertension in the parents and proteinuria in their diabetic offspring. The level of excretion used to define proteinuria (protein-to-creatinine ratio ≥ 0.5 g/g), however, while highly specific for renal disease, is not sensitive, and some parents whose hypertension was due to renal disease may have been included in the analysis. On the other hand, if hypertension is a clinical manifestation of inherited susceptibility to renal disease, inclusion of parents with proteinuria should not affect the relationship. In keeping with this assumption, the conclusions of the study were unchanged when parents with proteinuria and their offspring were included in the analysis (data not shown).

In conclusion, hypertension in both parents is a risk factor for proteinuria in the diabetic offspring. The underlying mechanism for this relationship remains to be determined, but the existence of factors that confer susceptibility to both hypertension and diabetic renal disease would provide an explanation for the present results.

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