Diabetic nephropathy in Surinamese South Asian subjects

Chandieshaw, P.K.

Een Hindostaanse arbeider voor zijn huis met gezin en buren, Suriname, ca. 1930.

Chapter 5

Renal disease in relatives of South Asian type 2 diabetic patients with end-stage diabetic nephropathy

Prataap K.Chandie Shaw[1], Leendert A. van Es[1], Leen C. Paul[1], Frits R. Rosendaal[2], John H.M. Souverijn[3], Jan P. Vandenbroucke[2]

1. Department of Nephrology, Leiden University Medical Center, The Netherlands
2. Department of Clinical Epidemiology, Leiden University Medical Center
3. Clinical Chemistry Laboratory, Leiden University Medical Center

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Abstract

Objective

South Asian immigrants in The Hague, The Netherlands, have a nearly 40-fold higher risk of end-stage diabetic nephropathy compared to the Dutch European population. To detect a genetic susceptibility for nephropathy within the South Asian population, we assessed whether familial clustering of nephropathy occurs in families of South Asian type 2 diabetic patients.

Research design and methods

We compared nephropathy prevalence between two groups of first-degree relatives of South Asian patients with type 2 diabetes; the first group (case-relatives) consisted of 169 relatives of patients with end-stage diabetic nephropathy; the second group (control-relatives) consisted of 161 relatives of diabetic patients who had no nephropathy. The case- and control-relatives were examined for diabetes, blood pressure, renal function, microalbuminuria and urine dipstick measurements.

Results

The mean age was 41 years and similar in the case- and control-relatives. Diabetes was distributed equally in both family groups. We did not find more nephropathy in first-degree relatives of South Asian type 2 diabetes patients with end-stage diabetic nephropathy in comparison with control-relatives.

Conclusions

We could not detect a genetic susceptibility for diabetic nephropathy within the South Asian population. The lack of familial clustering of renal disease in South Asian diabetic patients points to a general genetic or environmental susceptibility for diabetic nephropathy in this population.

Introduction

Familial clustering of diabetic nephropathy was first described in type 1 diabetic patients. [1] Later, clustering was also observed in type 2 diabetic patients. A familial predisposition for diabetic nephropathy was observed in different ethnic groups like the American Pima Indians, Afro-Americans, Brazilian and Italian type 2 diabetic patients. [2-7] These observations are consistent with the hypothesis of a genetic susceptibility in the pathogenesis of diabetic nephropathy.

South Asian persons from Suriname originally descent from the Indian subcontinent, including India, Pakistan, and Bangladesh. In a recent study, South Asian patients were found to have a close to 40-fold increased risk for end-stage diabetic nephropathy in comparison to native Europeans. [8] Studies performed in the UK showed comparable results. [9-10] This is higher than expected since the prevalence of type 2 diabetes was only eight times higher in the South Asian population, again in comparison with the Dutch European native population. [11] An explanation for this relatively higher incidence of diabetic nephropathy could be an additional genetic susceptibility to develop nephropathy within the South Asian population. This might be detected by the presence of familial clustering of nephropathy in relatives of patients with diabetic nephropathy, but specific family studies for nephropathy are lacking in the South Asian population. However, a small case-control family study in South India showed higher rates of proteinuria in siblings of type 2 diabetic patients with nephropathy in comparison with age, sex and diabetic duration matched siblings of control patients without diabetic nephropathy. [12]

The aim of our study was to investigate whether familial clustering of nephropathy occurs in first degree relatives of type 2 diabetic South Asian patients with and without nephropathy. We tried to prevent selection bias by a population-based study design and the testing of all non-diabetic relatives, with an oral glucose tolerance test.

Research design and methods

Study Design

In this study, we evaluated the predisposition for nephropathy among South Asian first degree relatives of type 2 diabetic patients with end-stage renal failure (**case-relatives**). They were compared with first-degree relatives of South Asian type 2 diabetic patients who had no clinical signs of diabetic nephropathy (**control-relatives**).

The case- and control-relatives were invited for an assessment (see below) between September 1, 1998 and December 31, 2000.
The study protocol was approved by the Institutional Medical Ethics Committee in accordance with the Declaration of Helsinki.

Subjects

Case-families

The case-index patients were recruited from the records of the dialysis units of three regional hospitals, which together represent the total dialysis capacity in the town of The Hague. Included were all patients first registered between 1990 and 1999 for dialysis because of end-stage renal failure attributed to type 2 diabetes; patients were considered to have type 2 diabetes if they used oral antidiabetic medication prior to dialysis, or if their fasting C-peptide levels were indicative of type 2 diabetes. South Asian dialysis patients were initially identified by their surnames. If the patients were alive, we visited them in the dialysis unit and confirmed their ethnic origin. A standardized interview was taken with respect to diabetes and family history as well as demographic parameters. After informed consent, we contacted their first-degree relatives living in the Netherlands (parents, siblings and children). If the case-index patient had died, we contacted the relatives with the help of the general practitioner (GP) of the deceased patient.

Control-families

Control-index patients with type 2 diabetes were selected with the help of general practitioners (GP) of the included case-index patients. For each case-index patient included, one South Asian control-index was chosen at random among the patients with type 2 diabetes from the records of the GP; control-index patients were eligible if they were of the same sex as the case-index and had no microalbuminuria. To ensure random sampling, we went through all the records of that GP, and made a numbered list of all eligible South Asian type 2 patients. Subsequently, control-index patients were drawn from this list by use of a random number table. Another source of control-index patients were the spouses of the investigated relatives. If the spouse had type 2 diabetes mellitus and no microalbuminuria, we invited the siblings and parents of the spouse for the investigation. The control-index patients were also invited through a letter for a visit at our outpatient's research unit. A few days later they were contacted by phone for informed consent and an appointment at our research outpatient clinic.

Inclusion of the family relatives

All first-degree relatives (father, mother, siblings, and children) of the case- and control-index patients living in the Netherlands were invited as part of a family investigation for diabetes and renal disease. We invited the case- and control-relatives randomly throughout the investigation period. Relatives who were pregnant were invited later on, three months after they gave birth. Patients younger than 16 years were not included. We tried to avoid appointments during the menstrual period of women.

Procedures and Measurements

The family relatives came during the morning hours, after fasting for at least 8 hours. Fasting venous blood samples were drawn for hemoglobin, creatinine and lipid profile. The relatives brought an early morning urine sample for quantitative measurements of albuminuria and dipstick urine analysis. They stayed in a quiet room and the blood pressure was measured three times after 5 minutes rest in sitting position using an OMRON 705CP automatic oscillometric blood pressure device. The cuff was placed at the right upper arm. If the circumference of the arm exceeded 32 cm, a large cuff was used. The weight and height were recorded in underwear. Also the circumference measurements of the waist and hip were performed. If the relatives did not use antidiabetic medication, an oral glucose tolerance test was done with 75 gram glucose and the fasting glucose as well as two hour glucose was measured. The renal function was estimated using the Cockcroft-Gault estimation. [13] We used a questionnaire to obtain data on general demographic variables (age, sex, educational level and marital status) family history of diabetes mellitus in first-degree relatives (age of onset, duration, treatment), hypertension, smoking and medication.

Laboratory measurements

Urinary albumin and protein were measured by immunoturbidimetric assay on a Hitachi 911, as was the HDL-cholesterol in serum. Glucose, creatinine, cholesterol and triglycerides were measured on a Hitachi-747 (Hitachi Tokyo, Japan). HbA1c was measured using the HPLC method with a Variant analyzer, Biorad, Hercules, CA, USA. Variance Coefficient 1.5% at different levels. The reference values for HbA1c are between 4.3 and 6.3%. Urine dipstick investigation for leukocyturia and hematuria was performed with patch test strips using reflectance photometry with a Miditron photometer (Boehringer Mannheim-Roche, diagnostics). [14]

Outcome measurements

Patients who currently used oral antidiabetics or insulin were classified as known diabetics. All other patients had a glucose tolerance testing (GTT) using the classic WHO criteria. [15] If the fasting blood glucose was higher than 7.8 mmol/L or two-hour GTT value was higher than 11.1 mmol/L, patients were coded as de novo-diabetic patients. If the fasting blood glucose was below the 7.8 mmol/L and two-hour GTT value was between 7.8-11.1 mmol/L, they were coded as impaired glucose tolerance. If the two-hour GTT value was below the 7.8 mmol/L, patients were classified as normoglycemic. Urine albumin concentration was measured in relation to the creatinine and expressed as ratio of albumin/creatinine in mg/mmol. Microalbuminuria was defined according to the diabetic standards. Normoalbuminuria was present if the albumin/creatinine ratio was < 2.5 in males and < 3.5 in females. Microalbuminuria was present if the ratio was between 2.5 and 36 for males and between 3.5 and 40 for females. Proteinuria was defined if the ratio was above 36 for males and 40 for females. The renal function was estimated using the Cockcroft-Gault formula and normalized for BSA of 1.73 m^2. The results of the urine dipstick were measured using qualitative test strips which were coded using an automated photometric reader. Leukocyturia was registered as absent, trace or positive; hematuria was registered as absent, trace or positive. During this visit, patients showed their medications. In case the patient forgot to bring the prescribed medication or medication card, the GP was contacted for the exact medication. Patients who did not use antihypertensive medication were coded as normotensive if the average blood pressure was below the 160 mmHg systolic and below the 90 mmHg diastolic. Borderline hypertensive profile was defined as diastolic blood pressure between 90 to 95 mmHg and systolic blood pressure below the 160 mmHg. If patients used antihypertensive medication or had average blood pressure above the 160 mmHg systolic or 95 mmHg diastolic, they were registered as hypertensive profile.

Statistical Analysis

The calculations for the study size were based on a minimally detectable relative risk of 3 for microalbuminuria in relatives of South Asian diabetics with renal failure versus South Asian diabetics without renal failure, with a type 1 error of 0.05 and a power of 0.90. Based on studies in the United Kingdom [9] and the Netherlands, [11] we assumed the diabetes mellitus prevalence in South Asian families at 20-30 percent). Assuming a prevalence of microalbuminuria in the family members of the controls at 7 percent, 150 relatives have to be included in each family group (of whom about

40 would expect to suffer from diabetes mellitus). For statistical comparison of the difference of means, e.g. age, duration of the diabetes, laboratory values between the case- and control-group, the Student's t-test was used; the measured difference of the means were expressed with 95% confidence intervals and P-values. Differences of categorical variables like glucose tolerance, urine dipstick measurements were expressed as percentage difference with 95% confidence intervals and as Chi-Square P-values.

Results

Recruitment of Index-patients

The recruitment of the index patients is shown in **Table 1.** We contacted 57 index patients with type 2 diabetes mellitus and end-stage diabetic nephropathy. Of these patients 20 were not eligible: 4 could not be reached by telephone or by mail, 1 had no potential relatives for investigation, and 15 patients did not give permission to contact their relatives, leaving 37 case-index patients.

Table 1: *Recruitment and drop-out reasons of the Index patients.*

	Case-index patients	Control-index patients
Contacted Index patients	**57**	**132**
Not reached index patients	4 (7.0%)	26 (19.7%)
No potential family members	1 (1.8%)	15 (11.3%)
No Informed consent	15 (26.3%)	31 (23.5%)
Microalbuminuria (control-index patient)	NA	17 (12.9%)
Eligible index patients	**37 (64.9%)**	**43 (32.6%)**

We contacted 132 control-index patients with type 2 diabetes mellitus and no microalbuminuria according to the records of the GP's. We could not reach 26 patients because they did not respond on our invitation and could not be reached by phone. Fifteen patients had no first-degree relatives living in the Netherlands and 31 control-index patients did not approve to contact their relatives. We therefore investigated 60 index control patients. Seventeen index control patients were excluded afterwards because they had microalbuminuria, leaving 43 eligible control-index patients for the study

Basic characteristics of the case- and control-index patients are given in **Table 2.** The age at inclusion for our investigation was slightly higher in the case-index patients group than in the control-index group. The case-index patients with end-stage diabetic nephropathy also had a longer duration of diabetes disease than the control-index patients who had no nephropathy (difference 4.6 years with 95% CI 0.9 to 8.4). The index patients with diabetic nephropathy were more often treated with insulin therapy.

Table 2: *Basic characteristics of the eligible index patients with type 2 diabetes mellitus.*

	Case-index patients	Control-index patients	Difference (95 % CI)
Number	37	43	
Males n (%)	43%	42%	1 (-20 to 23)
Age at inclusion investigation (years)	56.1	52.5	3.6 (-1,2 to 8.5)
Age at diagnosis diabetes (years)	38.7	39.0	-0.3 (-5.64 to 5.1)
Mean diabetes duration (years)	17.2	12.6	4.6 (0.9 to 8.4)
Insulin treated (%)	62.2	48.8	13.4 (8.3 to 34.9)

Recruitment of first-degree relatives

The recruitment of the 330 first-degree (siblings, children, parents) relatives was similar in families of index-case and index-control patients. Recruitment was done in 37 case families and 43 control families. The reasons and numbers of patients who did not participate in the study were distributed equally between the case- and control-group. In the case-group 234 relatives were approached; 65 patients (27.8%) declined or were unreachable, giving 169 case-relatives for our investigation. In the control-group 221 relatives were approached; 60 patients (27.2%) declined or were unreachable, giving 161 control-relatives for the present investigation.

Characteristics of the relatives

The basic characteristics are displayed in **Table 3.** Mean age was similar in the case and control families, about 41 years. There was a female preponderance in both family groups. Mean body mass index, body surface area, waist-hip ratio measurements and lipid profiles were equal in the case and control-relatives. In the case-family members, 19 (11.2%) were known diabetic patients. The amount of known diabetic relatives in the control-family members was higher (n = 28; 17.4%). The results of the glucose

tolerance testing according to the WHO criteria among the remaining relatives were similar.

Table 3: *Basic characteristics of first-degree relatives of diabetic index patients with and without nephropathy. The characteristics are expressed as means, unless otherwise stated.*

	Case-relatives	Control-relatives	Difference (95 % CI)	P-value
Age	41.5	40.7	0.8 (-1.8 to 3.3)	0.55
Male (%)	37.9%	44.7%	-6.8 (-17.5 to 3.7)	0.21
Body mass index (kg/m^2)	26.56	26.63	-0.07(-1.1 to 0.9)	0.89
Body surface area (m^2)	1.76	1.80	-0.04 (-0.1 to 0.06)	0.09
Waist-Hip ratio	0.92	0.93	-0.01 (-0.03 to 0.2)	0.39
Cholesterol	5.2	5.1	0.1 (-0.13 to 0.3)	0.45
HDL-Chol/Cholesterol ratio	4.21	4.24	-0.03 (-0.3 to 0.2)	0.85
Triglycerides	1.51	1.68	-0.17 (-0.5 to 0.1)	0.29
HbA1c (%)	5.59	5.75	-0.16 (-0.5 to 0.2)	0.31
Glucose tolerance testing (GTT)				
De novo DM	**13%**	**8.1%**	4.9 (-1.6 to 11.5)	0.22
Impaired GT	**8.9%**	**10.6%**	-1.7 (-8.1 to 4.7)	
Normoglycemia	**66.9%**	**64.0%**	2.9 (-7.4 to 13.2)	
Known DM	**11.2%**	**17.4%**	-6.2 (-13.7 to 1.4)	
Age (years)	53.8	52.9	-0.1 (-5.8 to 7.6)	
Insulin usage (%)	52.6	17.9	34.7 (8.2 to 61.3)	
Diabetes duration (years)	10.5	10.0	0.5 (-4.6 to 5.5)	
HbA1c (%)	8.26	8.01	0.25 (-0.7 to 1.2)	

Life style characteristics of the 330 relatives are shown in **Table 4**. There were no differences in numbers of smokers between the case- and control-relatives. There were slightly more subjects with vegetarian eating habits and Muslim religious attitudes in the control families. The level of education distributed equal in both case- and control relative family groups. The number of divorced persons was significant higher in the case group.

Blood pressure profiles and treatments are given in **Table 5**. The mean blood pressure measurements were equal in both the case and control-relatives. Antihypertensive medical treatment was used in 13% of the case-relatives and 15% of the control-relatives. The distribution of the type of antihypertensive medication was not different in both groups, especially for the ACE-inhibitor and Angiotensin 2 receptor blockers usage.

Table 4: Life style in 330 first degree family relatives.

	Case-relatives	Control-relatives	Difference (95 % CI)	P-Value
Smoking (%)				
Never	63.9	59.7	4.2 (-6.4 to 14.7)	0.32
Stopped	7.1	11.9		
Yes	29.0	28.3		
Vegetarian eating pattern (%)				
No	95.9	84.3	11.6 (5.2 to 18.0)	0.004
Only no meat or fish	4.1	14.5		
No meat, fish, dairy products or eggs	0.0	1.3		
Religion (%)				
Hindu	75.7	63.5	12.2 (2.3 to 22.1)	0.033
Muslim	20.1	27		
Christian	1.8	1.9		
Other or no religion	2.4	7.5		
Education (%)				
Primary school	23.7	19.3	4.4 (-4.4 to 13.3)	0.24
Lower general/vocation	17.8	13.6	4.2 (-2.4 to 13.0)	
Intermediate and higher general/vocation	48.4	54.1	-6.0 (-16.3 to 5.3)	
Higher vocation/University	10.1	13.0	-2.9 (-9.9 to 3.9)	
Marital Status (%)				
Maried	41.4	52.8	-11.4 (-22.1 to -0.6)	0.086
Unmarried	23.7	25.5	-1.8 (-11.1 to 7.5)	
Widowed	5.9	5.0	0.9 (-3.9 to 5.8)	
Divorced	23.1	12.4	10.7 (2.5 to 18.8)	
Unknown	5.9	4.3	1.6 (-3.1 to 6.3)	

Table 5: Blood pressure and treatment of hypertension in 330 family relatives.

	Case-relatives	Control-relatives	Difference (95 % CI)	P-value
Systolic blood pressure (mean, mmHg)	127.1	126.6	0.5 (-4.1 to 5.1)	0.83
Diastolic blood pressure (mean, mmHg)	79.3	79.7	-0.4 (-2.84 to 2.1)	0.75
Blood pressure profile (%)				
Normotensive profile	73.4	73.3	0.1 (-9.5 to 9.6)	0.64
Borderline hypertensive profile	4.1	5.6	1.8 (-4.8 to 9.6)	
Hypertensive profile	9.5	6.2		
Antihypertensive use	13.0	14.9	-1.9 (-9.4 to 5.6)	
Antihypertensive medication use (%)				
ACE-inhibitors	23.9	20.0	3.9 (-13.6 to 21.4)	0.65
AII-antagonists	0.0	5.0	-5.0 (-11.8 to 1.7)	
Diuretics	26.1	17.5		
ß-blockers	23.9	20.0	1.1 (-17.1 to 19.3)	
Ca- antagonists	21.7	27.5		
Other	4.4	10.0		

Clinical features of renal disease in first-degree relatives

The features of renal disease are given in **Table 6**. No differences were detected in the distribution of microalbuminuria and proteinuria among the case- and control-relatives. Subgroup analysis for diabetic state according to the WHO-criteria also showed no differences for microalbuminuria between the two family groups. Also serum creatinine values and estimated renal clearances were equal in both groups.

In general, there was no difference in dipstick readings between the case- and control-relatives.

***Table 6**: Clinical features of renal disease in 330 first-degree relatives of Type 2 diabetic patients with and without diabetic nephropathy.*

		Case-relatives	Control-relatives	Difference (95 % CI)	P-value
Albuminuria distribution (%)					
Normoalbuminuria		88.7	88.8	0.1 (-6.7 to 6.9)	0.81
Microalbuminuria		7.7	8.7		
Proteinuria		3.6	2.5		
Renal function creatinine (µmol/l)		83.7	82.7	1.0 (-3.1 to 5.0)	0.63
Cockcroft-Gault renal clearance/1.73 m^2		92.6	94.5	-1.9 (-6.4 to 2.5)	0.39
Urine dipstick readings					
Hematuria (%)	Absent	82.8	80.1	2.7 (-5.7 to 11.1)	0.02
	Trace	10.1	5.6	4.5 (-1.3 to 10.2)	
	Positive	7.1	14.3	-7.2 (-13.8 to -0.53)	
Leukocyturia (%)	Absent	63.9	68.3	-4.4 (-14.6 to 5.8)	0.42
	Trace	23.7	18.6	5.1 (-3.7 to 13.8)	
	Positive	12.4	13.1	-0.7 (-7.8 to 6.6)	

Discussion

In this population-based family study, we found no difference in the prevalence of nephropathy in family members of South Asian type 2 diabetes patients with and without nephropathy.

Recently, we reported a close to 40-fold higher risk of end-stage nephropathy due to type 2 diabetes mellitus in Surinamese South Asian immigrants when compared to native Dutch individuals. [8] This is much higher than the eight-time higher prevalence of diabetes [11] in this population. This supports the hypothesis of a higher susceptibility to develop diabetic nephropathy in the South Asian diabetic population. Another

possibility is faster progression of diabetic nephropathy towards end-stage renal failure in South Asian diabetic patients. Earlier studies for progression of nephropathy in South Asian diabetics were not conclusive. [16-17] An ethnic predisposition for renal diseases can emerge in two ways: a general susceptibility of the entire South Asian population or a familial predisposition for renal diseases within certain South Asian families. The latter would point towards shared environmental risk factors in these families or could indicate susceptibility genes for nephropathy which are inherited independently from diabetes mellitus.

In the present study, we investigated nephropathy in first-degree relatives of South Asian type 2 diabetic patients who had end-stage diabetic nephropathy necessitating dialysis treatment or in whom preparations for dialysis were made. As controls we invited first degree relatives of South Asian type 2 diabetic patients who did not have microalbuminuria. Despite the fact that we took the most pronounced renal disease patients as case-index patients, we did not detect differences in renal disease in their relatives, defined by micro-albuminuria, glomerular filtration rates and blood pressures. The familial predisposition for type 2 diabetes measured by GTT was similar in both the case- and control-relatives. There were no differences in the prevalence of newly discovered diabetics and impaired glucose tolerance test. Diabetic state, blood pressure profiles, antihypertensive treatment were the same in both groups. Urine dipstick measurement for leukocyturia and hematuria were similar in the case- and control-relatives. A difference was noted in religions. The control group had somewhat more Muslims than Hindu's which could explain the slightly higher percentage of vegetarians in the control group. However, this could only lead to less proteinuria in the control group.

The main advantage of our study is the investigation of all the diabetic family members, including previously unidentified diabetic family relatives. This appeared to be important because for every known diabetic relative, a new diabetic relative was discovered. Diabetes was the strongest risk factor for renal disease in both family groups. To prevent bias we randomly selected the control-index patients using the records of GP's of our case-index patients. Furthermore, we invited the relatives of the case families and control families in the same way.

The findings in our study are different from other studies in other ethnic populations with type 2 diabetic patients. In American Pima Indians, there is a higher risk of diabetic nephropathy in diabetic siblings and offspring if the index patient had diabetic nephropathy. [3] This was also found in families of Afro-American, Italian and Brazilian patients with type 2 diabetes. [4-7] However, the results of these studies cannot

be extrapolated directly to the South Asian population living in the Netherlands. Firstly, most studies were done with relatives of known diabetic patients only as controls. To study the hypothesis of familial nephropathy, we also took the results of newly discovered diabetic family members into account. Secondly, nearly all studies used proteinuric diabetics as case-index patients. We investigated relatives of case-index patients on dialysis treatment, giving a stronger contrast with the relatives of control-index patients. It could be argued that the number of diabetics in our study was not large enough to have sufficient power for detecting a clustering of diabetic nephropathy. However, given perfect equality in the degree of albuminuria and the prevalence of nephropathy patients in both groups, it is difficult to imagine that this would dramatically change with a larger sample size.

Conclusions

In the present investigation we did not find familial clustering of renal disease in families of type 2 diabetic patients with end-stage diabetic nephropathy. In an earlier study the much higher incidence of diabetic nephropathy in South Asians is not simply due to the higher incidence of diabetes. The “gap” between the 40-fold increase in diabetic nephropathy and the only 8-fold increase of diabetes itself may mean that all persons of South Asian descent are especially vulnerable to develop nephropathy once they have developed diabetes mellitus. Another possibility is faster progression of nephropathy towards end-stage diabetic nephropathy in this population. Future investigations should focus on the development and progression of diabetic nephropathy in South Asian type 2 diabetics.

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