STUDIES ON DIABETIC NEPHROPATHY AND SECONDARY DISEASES IN TYPE 1 DIABETES

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ABSTRACT

Present study on diabetic nephropathy was carried out on 548 patients of which 311 (56.75%) were male and 237 (43.25%) were female. Patients suffering from type-1 diabetes were studied for nephropathy. Of the total patients, 195 (35.58%) were of type-1 of which 115 (58.97%) were males and 80 (41.03%) were females. Mean age at diagnosis of nephropathy in type 1 patient was 52.01±0.41 years, which shows that the type 1 nephropathy patients were inflicted with the disease at an early age. Mean body mass index estimated in type 1 nephropathy patients is 26.49 ± 0.23 Kg/m^2. For the diagnosis of nephropathy different clinical tests were also recorded. The estimations were, 158.15±1.93mg/100ml mean blood urea, 6.94±0.07mg/100ml mean blood creatinine, 337.38±4.57mg/100ml blood glucose level, 6.62±0.09mmol/lit potassium level and 158.13±1.16 mmol/lit sodium level. In type 1 nephropathy patients microalbuminuria (30-300 mg/day) was found in 51.28% and macroalbuminuria (>300 mg/day) was present in 48.72%. Secondary diseases associated with diabetic nephropathy in type 1 are retinopathy, blood pressure, diabetic foot and neuropathy. The highest percentage of IDDM nephropathy (IDDMN) patients were those who had attained no school education and the lowest percentage were those who attained education of university level. As for socio-economic status, the highest percentage (25.22%) of IDDMN patients was of skilled personnel. Calculated coefficient of inbreeding (F) was 0.031 for IDDMN. It is suggested that both genetic and non-biological factors like socio-economic status and education play a role towards the infliction of type-I nephropathy.

KEY WORDS: Nephropathy; Albuminuria; Type 1 diabetes.

INTRODUCTION

Diabetes mellitus is a condition in which there is a chronically raised blood glucose concentration. It is caused by an absolute or relative lack of the hormone insulin, i.e., insulin is not being produced from the pancreas or there is insufficient insulin for the body need (1,2). One of the most important clinical features of diabetes is its association with chronic tissue complications. These generally occur after several years of diabetes and affect the small blood vessels (microangiopathy) in the kidney, eye and nerves. Microangiopathy at least is thought to be related to the duration and severity of hyperglycemia (2).

Type-1 or insulin dependent diabetes mellitus (IDDM) mainly appears in early adult life. Diabetic nephropathy occurs in approximately one third of individuals with type-1. Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria, a relentless decline in GFR (Glomerular Filtration Rate), raised arterial blood pressure and increased relative mortality for cardiovascular diseases. This follows with a more rapid progression of other secondary complications, (retinopathy, neuropathy, diabetic foot and blood pressure) (3,4).

The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels (>30 mg/day) of albumin in the urine, referred to as microalbuminuria, and patients with microalbuminuria are referred to as having incipient nephropathy (5,6). Diabetic nephropathy is a leading cause of end stage renal failure. Epidemiological and family studies have demonstrated that only a subset of patients develop this complication, where family clustering of nephropathy is present. Ethnicity also plays an important role in the risk of developing this kidney disease (7).

High mortality in nephropathy is due to an excess of cardiovascular mortality (8,9) and to end stage renal failure (10,11). Development of nephropathy in type-1 patients may be identified accurately by the detection of microalbuminuria (7). Albuminuric diabetics may be 20 times more likely to die of cardiovascular disease than non-albuminuric ones (5). The relationship between arterial blood pressure and

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diabetic nephropathy seems to be a complex one, nephropathy increasing the blood pressure and blood pressure accelerating the course of nephropathy (7).

Genetic susceptibility contributes significantly to the risk of developing nephropathy in type-1 diabetes, and genetic components of the renin angiotensin system are possible candidates (12-14). Familial predisposition to essential hypertension increases the risk of diabetic nephropathy (15,16). It has been repeatedly demonstrated that the susceptibility of a diabetic to future renal failure is best predicted by the presence or absence of renal disease in their diabetic relatives. The familial clustering of diabetic nephropathy is of far greater predictive value than is the level of blood pressure or glycemic control. In type 1 patients, the presence of hypersensitive relatives increases the risk for development of diabetic nephropathy (17). This familial clustering of diabetic renal disease susceptibility clearly suggests that in addition to the inherited and environmental factors that produce hyperglycemia, the predisposition to nephropathy is under independent genetic control (i.e., diabetic nephropathy gene exists). Although diabetic nephropathy is prevalent among all individuals with type-1 (35% lifetime risk), it is extremely common among those with diabetic nephropathy siblings (71% lifetime risk) (17). Genes involved in blood pressure regulation are logical candidates for diabetic nephropathy susceptibility. Although, the genetic basis of hypertension is still unfolding, many studies have suggested putative hypertension susceptibility genes. One widely studied example is the angiotensinogen gene (AGT) on chromosome 1 (18).

The present study was carried out to provide baseline information about diabetic nephropathy regarding age at diagnosis, familial occurrence, any association with other disease, its mode of inheritance (whether it shows Mendelian inheritance or familial clustering or both in this study), the influence of social status and education on diabetic nephropathy occurrence and also how marriage types affect the appearance of diabetic nephropathy.

MATERIALS AND METHODS

Different hospitals were visited to contact a large number of diabetic nephropathy patients for the collection of data. Patients were also visited at their homes to collect more detailed information. The data were collected from main hospitals in the N.W.F.P, especially from Peshawar and Swat. Some data were also collected from Islamabad. For this purpose, the hospitals were visited during the period of June 1999 to March 2000.

The hospitals visited were as follows: Hayatabad Medical Complex, Peshawar, Post Graduate Institute Lady Reading Hospital, Peshawar, Hayat Shaheed Teaching Hospital, Peshawar, Saidu Medical Complex, Swat and Federal Government Services Hospital, Islamabad.

A total of 548 patients were interviewed for data collection, of which, 311 were males and 237 were females. For data collection, specific questionnaire was used which included variety of questions, such as: present age of the patient, age at diagnosis of nephropathy, age at diagnosis of diabetes, total duration of diabetes, familial relationship between husband and wife, familial relationship between the parents of patients, family history regarding the same or any other disease, the information regarding different clinical tests done for the diagnosis of nephropathy and information about the socio-economic position (occupation), education and life style of the patients.

Occupations were grouped into different categories according to their faculties. These categories are shown below.

C-I Professional and management.
C-II Intermediate.
C-III Skilled (non-manual).
C-IV Skilled (manual).
C-V Partially skilled.
C-VI Unskilled.

Familial relationships in marriages of patients and their parents were classified as: First cousin (IC), Distant relation (DR), Braderi (BR) and Unrelated (UR).

Parameters like height (in meters) and weight (in kg) of patients were analyzed to check their link with disease prevalence and incidence.

The clinical tests done for the diagnosis of nephropathy included blood urea, blood creatinine, blood glucose, sodium, potassium and albumin. The blood glucose was taken randomly.

The statistical analysis carried out for this study includes mean, standard error, number of studied samples (n), t-test and percentage (%). Mean co-

efficient of inbreeding (F) was also calculated following Wright's (1992) method (19).

177 normal subjects were also interviewed for comparison between the nephropathy patients and normal subjects. These controls were normal only from the diabetes and diabetic nephropathy point of view.

RESULTS

Present study is based on 548 patients diagnosed with diabetic nephropathy (DN). Out of total 548 patients examined 311(56.75%) were males and 237(43.25%) were females. A total of 177 normal subjects were also interviewed as control, out of which 98(55.37%) were males and 79(44.63%) were females. Of the total patients examined 195(35.58%) were diagnosed with Insulin dependent diabetes mellitus (IDDM) nephropathy. In IDDM-nephropathy patients, 115(58.97%) were males and 80(41.03%) were females.

Mean present age of male IDDMN patients was 53.42±0.50 years, and that of females was 53.58±0.77 years, while collectively it is 53.48±0.43 years. The age at diagnosis of diabetic nephropathy in male patients was 52.04±0.47 years and in female patients was 51.96±0.71 years, while the collective age at diagnosis for both sexes was 52.01±0.41 years.

Age of onset of diabetes in IDDMN patients was 38.84±0.36 years. In male IDDMN patients, diabetes was diagnosed at 38.53±0.43 years, and in females at 39.26±0.64 years. The duration of diabetes in IDDMN patients was 13.19±0.21 years after which they were diagnosed with diabetic nephropathy. The duration of diabetes in male patients was 13.56±0.28 years, and in female patients it was 12.68±0.32 years. The total duration of diabetes in male patients was 14.97±0.31 years, and in female patients, it was 14.29±0.37 years and that of sexes combined was 14.69±0.24 years. Mean body mass index (BMI) in diabetic nephropathy patients was 26.49±0.23 kg/m^2. Mean BMI in male patients was 25.19±0.23 kg/m^2, and in female patients was 28.37±0.35 kg/m^2. In the control sample, BMI in males was 24.69±0.17 kg/m^2 and in females 26.05±0.19 kg/m^2. The difference of mean BMI in males and females patients compared to control males and females was 2.32 and 0.5 kg/m^2 (Table 1).

Table1. IDDMN Patient's Age at Time of Diagnosis

ITEM	SEX	MEAN (Year)	S.E	N
Age at present	M	53.42	0.50	115
	F	53.58	0.77	80
	Both	53.48	0.43	195
Age at diagnosis				
of diabetes	M	38.53	0.43	115
	F	39.26	0.64	80
	Both	38.84	0.36	195
Age at diagnosis				
of nephropathy	M	52.04	0.47	115
	F	51.96	0.71	80
	Both	52.01	0.41	195
Duration of diabetes				
leading to nephropathy	M	13.56	0.28	115
	F	12.68	0.32	80
	Both	13.19	0.21	195
Total duration of diabetes	M	14.97	0.31	115
	F	14.29	0.37	80
	Both	14.69	0.24	195
Body mass Index (BMI)	M	25.19	0.23	115
	F	28.37	0.35	80
	Both	26.49	0.23	195

The biochemical analysis of IDDMN patients for the estimation of blood urea, blood creatinine, blood sugar, sodium and potassium level and their mean estimations is shown in table 2.

Table 2: Biochemical Analysis of IDDMN Patients

ITEM	SEX	MEAN	S.E	N
Blood Urea	M	160.34	2.32	106
	F	154.92	3.32	72
	Both	158.15	1.93	178
Blood Creatinine	M	7.00	0.11	98
	F	6.85	0.10	70
	Both	6.94	0.07	168
Blood Glucose	M	335.53	5.85	115
	F	340.05	7.32	80
	Both	337.38	4.57	195
Sodium	M	160.87	1.29	90
	F	153.49	2.09	53
	Both	158.13	1.16	143
Potassium	M	6.69	0.10	86
	F	6.51	0.17	52
	Both	6.62	0.09	138

Secondary diseases to diabetic nephropathy in IDDMN patients were retinopathy, blood pressure, diabetic foot, and neuropathy. Retinopathy was diagnosed in 57(29.23%) IDDMN males, and in 35(17.95%) females, in sexes combined 92(47.18%) were diagnosed. Blood pressure was diagnosed in 156(80%) IDDMN patients, of which 95(48.72%) were male, and 61(31.28%) were female patients. Diabetic foot was diagnosed in 84(43.08%) IDDMN patients, in which 53(27.18%) were male and 31(15.90%) were female patients. Neuropathy was diagnosed in 57(29.23%) IDDMN patients, in which 40(20.51%) were male, and 17(8.72%) were female patients (Table 3).

Table 3. Secondary Diseases to Diabetic Nephropathy in IDDM Patients

DISEASE	SEX	NUMBER	PERCENTAGE
Retinopathy	M	57	29.23%
	F	35	17.95%
	Both	92	47.18%
Blood Pressure	M	95	48.72%
	F	61	31.28%
	Both	156	80%
Diabetic Foot	M	53	27.18%
	F	31	15.90%
	Both	84	43.08%
Neuropathy	M	40	20.51%
	F	17	8.72%
	Both	57	29.23%

Table 4 shows distribution of IDDMN patients according to levels of education they have attained. The highest percentage 46.96% is of those patients who have not attained any school education, and the lowest percentage 6.96% is of those who attained education of university level.

Table 4. Distribution of IDDMN in Relation to Educational Level

EDUCATION	NUMBER	PERCENTAGE
None	54	46.96%
School	31	26.96%
College	22	19.13%
University	8	6.96%

Distribution of IDDMN patients in different categories of socioeconomic status (occupation) is shown in table 5. The highest percentage of patients is in skilled (non manual) (25.22%) and second highest category is of partly skilled (20.87%), and the lowest percentage of patients is in unskilled persons (9.57%).

Table 5. Distribution of IDDMN patients in Relation to Socioeconomic Status

OCCUPATION	NUMBER	PERCENTAGE
Professional and managerial	21	18.26%
Intermediate	19	16.52%
Skilled (non-manual)	29	25.22%
Skilled (manual)	11	9.57%
Partly skilled	24	20.87%
Unskilled	11	9.57%

The distribution of IDDMN patients according to their familial relationship is given in Table 6. Patients coming from first cousin parents are 49.23% and those coming from unrelated parents are 17.95%. Coefficient of inbreeding (F) calculated for IDDM-nephropathy patients was 0.031.

Table 6. Distribution of IDDMN among Familial Relationships

PATIENTS	IC	DR	BR	UR	TOTAL	COEF. OF INB. (F)
Males	61	17	16	21	115	
Females	35	18	13	14	80	
Total	96 (%)	35 (49.23)	29 (17.95)	35 (14.87)	195 (17.95)	0.031

Microalbuminuria (30-300 mg/day) was present in 100(51.28%) IDDMN patients, in which 56(28.72%) were males, and 44(22.56%) were females. Macroalbuminuria (>300mg/day) was found in 95(48.72%) IDDMN patients, in which 59(30.26%) were male, and 36 (18.46%) were female patients.

Table 7. Preralence of Micro and Macroalbuminuria in IDDMN Patients

ITEM	SEXES	NUMBER	PERCENTAGE
Microalbuminuria	M	56	28.72%
	F	44	22.56%
	Both	100	51.28%
Macroalbuminuria	M	59	30.26%
	F	36	18.46%
	Both	95	48.72%

DISCUSSION

Patients with diabetes account for approximately one-third of all end stage renal failure (ESRD) cases and number is increasing due to growing incidence of diabetes. Out of 14 million diabetes patients in the U.S, 5 – 10% were diagnosed with type 1. Diagnosis of DN relies on the detection of persistent proteinuria after more than 7 to 10 years of diabetes (10). The prevalence of microalbuminuria, proteinuria and renal failure in diabetes increases with increase in duration of diabetes. About 30% of type-1 diabetic patients have proteinuria after 20 years diabetes (2,21). The present study shows that IDDM patients develop nephropathy on average of 13.19 ± 0.21 years and 14.20 ± 0.20 years respectively after the diagnosis of diabetes. In this study, IDDMN patients showed prevalence of microalbuminuria at an average of 11.58±0.22 years and macroalbuminuria at an average of 14.89±0.28 years after diagnosis of diabetes.

According to Williams and Pickup (1999) hypertension is about twice as common in diabetic patients as in the non-diabetic population (2). The present study agrees with the above results as 80% of IDDMN patients have hypertension.

Widespread macrovascular disease, severe retinopathy and neuropathy usually accompany DN. The prevalence of retinopathy increases with duration of diabetes, with a few patients presenting with retinopathy in the first 5 years and 80-100% developing some form of this complication after more than 20 years duration (2). According to Joslin (1985) patients with DN may suffer simultaneously from a progressive retinopathy with visual failure (21). Thus diabetic renal-retinal syndrome results from long-standing progressive microangiopathy. There is considerable increase in the frequency of retinopathy as 75% of patients with advanced DN have proliferative retinopathy and 25-30% are blind (19). In the present study retinopathy was diagnosed in 47.18% of IDDMN patients.

Neuropathy is encountered in almost 20% of diabetes patients (23). Patients reaching advanced nephropathy develop diabetic neuropathy as well (19). In this study, about 29.23% of IDDMN patients, developed neuropathy. As a result of the development of neuropathy in DN patients foot problems like foot ulcers, and digital gangrene also arise (2,16). There are 45.62% diabetic foot DN patients in the whole sample of the present study. Out of these 43.08% are IDDMN.

The socioeconomic status of patients also affects development of diabetes and DN. According to Shami *et al* (24), low-income employees and small shopkeepers are mostly affected with diabetes. Results from the present study also agree with the above results. Most of the low-income patients (shopkeepers, farmers and labor) develop DN.

In the present study the IDDMN patients coming from first cousin (IC) parental relationship are 49.23%, and those coming from unrelated are 17.95% and the coefficient of inbreeding (F) for this is 0.031.

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