STUDIES ON DIABETIC NEPHROPATHY AND SECONDARY DISEASES IN TYPE 2 DIABETES

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ABSTRACT

Present investigations include 548 diabetes mellitus patients of which 311 (56.75%) were male and 237 (43.25%) were female patients. Type 2 nephropathy patients totalled 353(64.42%) of which 196(55.52%) were males and 157(44.48%) were females. Mean age at diagnosis of type 2 nephropathy patients was 61.64±0.48 years. Mean body mass index (BMI) estimated in type 2 nephropathy patients was 26.77±0.15 Kg/m^2. Biochemical evaluations in type 2 nephropathy patients was as follows: mean blood urea 156.02±1.48mg/100ml, mean serum creatinine 6.91±0.06mg/100ml, mean blood glucose level 339.39±3.34mg/100ml, potassium 6.81±0.06 Mmol/Lit and mean sodium was 157.44±0.77Mmol/Lit. Microalbuminuria was found in 43.63% and the remainder had macroalbuminuria. Secondary diseases associated with diabetic nephropathy in type-2 nephropathy were retinopathy, hypertension, diabetic foot and neuropathy. The highest percentage of type 2 nephropathy (type2N) patients were those who had no school education and the lowest percentage was of those who had education of university level. As far as socio-economic status was concerned, the highest percentage (25.22%) of type2N patients was of skilled personals. Calculated coefficient of inbreeding (F) for type2N patients was 0.028.

KEY WORDS: Type 2 diabetes; Nephropathy; Albuminuria

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 insulin, i.e., insulin is not being produced from the pancreas or there is insufficient insulin for the body's need. Type 2 diabetes usually starts in middle age or later. It is the common type of diabetes and is thought to be due to both impaired insulin secretion and resistance to the action of insulin at its target cells. 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 kidneys, eyes and nerves. Microangiopathy at least is thought to be related to the duration and severity of hyperglycemia (1).

Diabetic nephropathy occurs in approximately one third of individuals with type 2 diabetes (2). 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).

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. Diabetic nephropathy is a leading cause of end stage renal failure. The pathogenesis of diabetic nephropathy is multifactorial with contribution from metabolic abnormalities, homodynamic alteration, and various growth factors and genetic factors. Epidemiologic and family studies have demonstrated that family clustering and ethnicity plays an important role in the risk of developing this kidney disease (4). It is estimated that up to 50% patients with diabetes mellitus will develop renal failure (5). It is now firmly established that diabetic nephropathy is associated with high morbidity and mortality (6). There is marked heterogeneity in the clinical picture seen in long termed diabetes as some diabetic patients even with poor metabolic control may not develop clinical diabetic nephropathy (7).

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High mortality in nephropathy is due to an excess of cardiovascular mortality (8), and to end stage renal failure (9). Albuminuric diabetes patients are 20 times more likely to die of cardiovascular disease than are non-albuminuric ones (10). The relationship between arterial blood pressure and diabetic nephropathy seems to be a complex one, nephropathy increasing blood pressure and blood pressure accelerating the course of nephropathy (11). Type 2 diabetes mellitus and its long-term complications, such as nephropathy have a strong genetic predisposition. Insulin resistance is thought to be a pathogenic factor, predisposing genetically prone individuals to develop the microvascular complication of diabetes (12). In type 2, studies have 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. Familial aggregation of diabetic nephropathy has been reported in European (13) and American Whites (14) with type 2 diabetes patients.

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), the influence of social status and education on diabetic nephropathy and also how marriage types affect the appearance of diabetic nephropathy.

MATERIALS AND METHODS

Different hospitals were visited from June 1999 to March 2000 for the collection of data. Patients were also visited at their homes for this purpose. Data was collected from 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. 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, information regarding different clinical tests done for the diagnosis of nephropathy and information about the socio-economic status (occupation), education and life style of the patients.

Occupations were grouped into different categories according to their faculties in following manner: C-I Professional and Management; C-II Intermediate; C-III Skilled (Non-manual); C-IV Skilled (Manual); C-V Partially Skilled; and C-VI Unskilled.

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

Height and weight of the patients were studied in order to check their link with the prevalence of disease. Height was measured in meters while weight was recorded in kg. Clinical tests included blood urea, serum creatinine, blood glucose, sodium, potassium, and albumin. Statistical analysis like mean, standard error, number of studied samples (n), t-test and percentage (%) were also carried out during our study. Mean co-efficient of inbreeding (F) was calculated following Wright's (1992) method.

For control studies regarding diabetes and diabetic nephropathy, 177 normal subjects were interviewed to have a complete comparative analysis.

RESULTS

During present investigations, of the total diabetes patients examined, 353 (64.42%) were diagnosed as type 2 diabetes. Among type 2 diabetes patients 196 (55.52%) were males and 157 (44.48%) were females. Mean present age of male type 2 patients was 62.36±0.59 years, and that of females was 65.28±0.68 years, while for both the sexes it was 63.66±0.45 years. The age at diagnosis of diabetic nephropathy in male patients was 60.24±0.70 years, and in female patients was 62.71±0.60 years and it was 61.64±0.48 years for both the sexes. Diabetes in all type 2 patients was diagnosed at 47.12±0.33 years. In male type 2 patients diabetes was diagnosed at 46.09±0.43 years and in female patients at 48.41±0.49 years. The duration of diabetes in type 2 patients was

14.20±0.20 years after which they were diagnosed for diabetic nephropathy. The duration of diabetes in male patients was 14.12±0.27 years and in female patients was 14.29±0.29 years. The total duration of diabetes in type 2 patients was 16.48±0.24 years, and in male patients the total duration was 16.17±0.33 years while in female patients it was 16.88±0.36 years. Mean body mass index (BMI) in type 2 patients was 26.77±0.15kg/m^2. Mean BMI in male patients was 25.57±0.16 kg/m^2, and in female patients it was 28.27±0.21 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 male and female patients compared to control males and females was 2.22 and 0.88 kg/m^2 (Table 1).

Table 1: Basic Data of Type 2 Diabetes Patients with Nephropathy.

	SEX	MEAN	S.E	n
Age at present (years)	M	62.36	0.59	196
	F	65.28	0.68	157
	Both	63.66	0.45	353
Age at diagnosis of diabetes (years)	M	46.09	0.43	196
	F	48.41	0.49	157
	Both	47.12	0.33	353
Age at diagnosis of nephropathy (years)	M	60.24	0.70	196
	F	62.71	0.60	157
	Both	61.64	0.48	353
Duration of diabetes leading to nephropathy (years)	M	14.12	0.27	196
	F	14.29	0.29	157
	Both	14.20	0.20	353
Total duration of diabetes (years)	M	16.17	0.33	196
	F	16.88	0.36	157
	Both	16.48	0.24	353
Body Mass Index (BMI) (Kg/m^2)	M	25.57	0.16	196
	F	28.27	0.21	157
	Both	26.77	0.15	353

Biochemical analysis of type 2 patients included blood urea, serum creatinine, blood glucose, sodium and potassium level. Their mean values are shown in table 2.

Table 2:Biochemical Analysis of Type 2 Diabetes Patients

	SEX	MEAN	S.E	n
Blood Urea (mg/dl)	M	155.65	1.84	178
	F	156.58	2.46	118
	Both	156.02	1.48	296
Serum Creatinine (mg/dl)	M	6.82	0.09	176
	F	7.05	0.07	115
	Both	6.91	0.06	291
Blood Glucose (mg/dl)	M	336.33	4.58	196
	F	343.22	4.87	157
	Both	339.39	3.34	353
Sodium (Mmol/Lit)	M	157.93	0.93	150
	F	156.55	1.41	82
	Both	157.44	0.77	232
Potassium (Mmol/Lit)	M	6.84	0.08	150
	F	6.76	0.11	82
	Both	6.81	0.06	232

Secondary diseases associated with diabetic nephropathy in type 2 patients were retinopathy, blood pressure, diabetic foot and neuropathy. Retinopathy was diagnosed in 211 (59.77%) of type 2 patients, in which 116 (32.86%) were males, and 95(26.91%) were females. Blood pressure was diagnosed in 156(44.19%) male and 127 (35.98%) female patients out of 283 (80.17%) total diagnosed patients. Diabetic foot was diagnosed in 166 (47.03%) Type 2 patients in which 93 (26.35%) were males and 73 (20.68%) were females. Neuropathy was diagnosed in 103 (29.18%) Type 2 patients in which 45 (12.75%) were female, and 58 (16.43%) were male patients (Table 3).

Table 3: Secondary Diseases Associated with Diabetic Nephropathy in Type 2 Patients.

DISEASE	SEX	NUMBER	PERCENTAGE
Retinopathy	M	116	32.86
	F	95	26.91
	Both	211	59.77
Blood Pressure	M	156	44.19
	F	127	35.98
	Both	283	80.17
Diabetic Foot	M	93	26.35
	F	73	20.68
	Both	166	47.03
Neuropathy	M	58	16.43
	F	45	12.75
	Both	103	29.18

Distribution of type 2 patients according to levels of education they had attained is shown in table 4. The highest percentage 50.32% was of those patients who have not obtained any school education, and the lowest percentage 3.82% of those who had education of university level.

Table 4: Distribution of Type 2 Nephropathy in Relation to Level of Education

EDUCATION	NUMBER	PERCENTAGE
None	79	50.32
School	46	29.3
College	26	16.56
University	6	3.82

Socioeconomic status (occupations) wise distribution of type 2 patients is given in table 5. The highest percentage of patients was in the skilled (non-manual) category (23.98%); next highest category was of partly skilled (20.92%), while the lowest percentage of patients was in unskilled (9.69%) category.

Table 5: Distribution of Type 2 Diabetes in Relation to Socioeconomic Status

OCCUPATION	NUMBER	PERCENTAGE
Professional and managerial	37	18.88
Intermediate	32	16.33
Skilled (non-manual)	47	23.98
Skilled (manual)	20	10.20
Partly skilled	41	20.92
Unskilled	19	9.69

The distribution of type 2 patients according to their familial relationship is given in Table 6. Patients born from first cousin parents were 45.04% and those born of unrelated parents were 16.43%. Coefficient of inbreeding (F) calculated for type 2 patients was 0.028.

Table 6: Distribution of Type 2 Diabetes Patients Based on Different Familial Relationship

PATIENTS	IC	DR	BR	UR	TOTAL	COEF. OF INB. (F)
Males	99	40	26	31	196	
Females	60	30	40	27	157	
Total	159	70	66	58	353	0.028
(%)	(45.04)	(19.83)	(18.70)	(16.43)		

Microalbuminuria (30-300 mg/day) was found in 154 (43.63%) type 2 patients, of which 84 (23.8%) were males and 70 (19.83%) were females. Macroalbuminuria (>300mg/day) was found in the remainder, of which 112 (31.73%) were male, and 87 (24.65%) were female patients.

DISCUSSION

The study sample of 548 diabetic nephropathy patients (DN) was observed of which 353 were diagnosed as type 2 nephropathy. Patients with diabetes account for approximately one-third of all end stage renal failure (ESRD) cases and the number is increasing due to growing incidence of diabetes. Out of 14 million diabetes patients in the U.S, 90–95% of patients were diagnosed as type 2 diabetes. Majority of diabetic nephropathy patients on chronic dialysis had type 2 diabetes (60%) (15). The first reports of DN in late 19th and early 20th centuries described in patients with type 2 diabetes. Rodby (16) is of the view that patients with type 2 diabetes having ESRD are increasing. This is because the rate of growth in ESRD increases with increasing age (16). The ESRD patients are most pronounced in the age ranging from 65 to 74 years. The rate of increase in ESRD patients approximates 14-17% per year. The age at onset ESRD was 55 years in 1984 and by the year 1992 the age at onset for ESRD was delayed to 59 years, and the time of initiation of renal replacement therapy was 61 years. The mean age of diagnosis of all the patients in our study is 58.02±0.35 years. This is agreement with the finding of Rodby (16). It is observed that type 2 patients were diagnosed mainly in the age ranging from 45 to 54 years. This study also shows that the mean age of type 2 patients is 47.12± 0.33 years (17).

The prevalence of microalbuminuria, proteinuria and renal failure in diabetes increases with increase in duration of diabetes. The present study shows that in our cohort the duration of diabetes at the diagnosis of microalbuminuria was 15.85±0.26 years and 12.05±0.21 years for macroalbuminuria. According to estimates hypertension is about twice as common in diabetic

patients as in the non-diabetic population. About 30-60% of White type 2 diabetic patients develop hypertension (1). The present study agrees with the above results as 80% of our patients have hypertension.

Wide spread macrovascular disease, severe retinopathy and neuropathy usually accompany DN. The prevalence of retinopathy increases with duration of diabetes, with the few patients presenting with retinopathy in the first 5 years and 80-100% develops some form of this complication after more than 20 years duration (1). According to Joslin (18) patients with DN may suffer simultaneously from a progressive retinopathy with visual failure. Thus diabetic renal-retinal syndrome results from long-standing progressive microangiopathy. There is considerable increase in the frequency of retinopathy in that 75% of patients with advanced DN have proliferative retinopathy and 25-30% are blind (19). In the present study retinopathy was diagnosed in 59.77% of type 2 patients.

Neuropathy is encountered in almost 20% of diabetes patients. Patients having advanced nephropathy develop diabetic neuropathy as well (19). In our study 29.18% had neuropathy. As a result of the development of neuropathy in DN patients, foot problems like foot ulcers and digital gangrene also arise commonly (1, 19). In our study 47.03% had foot problems.

Diabetes and smoking interact to produce excess microvascular disease and mortality. Cigarette smoking is a major risk factor for the progression of diabetic nephropathy. In type 2 patients with newly diagnosed diabetes, albuminuria was found in 8.20% of smokers and in 7.30% of former smokers; however it was present in 2.10% of non-smokers (1, 16). Our study is in agreement with these results as there were 58.26% are smokers in our cohort

The socioeconomic status of patients also effect development of diabetes and DN. According to investigations, 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 laborers) develop DN (17).

Type 2 patients coming from the IC familial relationship are 45.04% and from unrelated are 16.43% and the coefficient of inbreeding (F) for type 2 parental relationship is 0.028. Coefficient of inbreeding (F) for type 2 nephropathy patients is very much near to the unit of general population (F=0.028; 16). It is suggested that both genetic and non-biological factors like socio-economic status and education play role towards the infliction of and type 2 nephropathies.

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