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Evaluation of Type of Nephropathy in Patients of Type-2 Diabetes Mellitus

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Abstract

Background of the Study, Aims and Objectives: There are very few studies on histological patterns of diabetic nephropathy in our part of country. The aim of this study was to evaluate the renal involvement in patients with Type-2 diabetes mellitus (T2DM), assess the histopathological changes and establish a clinico-pathological correlation. **Subjects, Method and Materials**: Thirty two Type 2 DM patients with nephropathy, after screening consecutive hundred(100) Type 2 Diabetics admitted to the Medicine Department were evaluated for renal involvement by kidney biopsy and histopathological study. Statistical analysis was done by student's t-test, chi-square and linear regression analysis. **Results:** Thirty two patients (32) with diabetic nephropathy (20 males and 12 females) formed the study group out of hundred (100) consecutive Type-2 diabetes mellitus patients (58 males and 42 females) admitted to Medicine Department of SCB Medical College Hospital, Cuttack. The frequency of occurrence of clinical diabetic nephropathy was 32%. Most of the patients were having duration of DM of 6-10 years (87.5%). Pedal edema was found in 96.87%, hypertension in 87.5% patients respectively. Regression analysis showed that durations of DM and HbA1c were the two significant risk factors ($P < 0.05$) for development of nephropathy. Histopathologically, diffuse glomerulosclerosis was the most common form of renal abnormality found in 93.75% followed by nodular glomerulosclerosis in 62.50% with overlap in many patients, membranous nephropathy in 12.5% and focal necrotising glomerulonephritis in 6.25% respectively. There was no statistically significant clinicopathological correlation observed between clinical and biochemical parameters in patients harbouring the two predominant histological types of nephropathy *i.e.* diffuse and nodular glomerulosclerosis with respect to age, sex, duration of diabetes, body mass index, systolic blood pressure, HbA1c, 24 hour urinary protein, creatinine clearance, serum urea, serum

creatinine or lipid profile. **Conclusion:** Durations of diabetes and HbA1c were found to be strongly associated with development of diabetic nephropathy. Diffuse glomerulosclerosis was the most common form of renal abnormality found in 93.75% followed by nodular glomerulosclerosis in 62.50% of patients.

Keywords

Type 2 DM, Diabetic Nephropathy, Renal Biopsy, Diffuse Glomerulosclerosis, Nodular Glomerulosclerosis

1. Introduction

The global burden of DM is enormous with an estimated 366 million people living with DM worldwide (2011) [1]. India accounted for nearly one sixth of global diabetes burden in 2011 with about 62 million of people affected by diabetes which is projected to rise to 101 million by 2030 [1] [2]. Type 2 diabetes mellitus (T2DM) is most prevalent form of DM seen in India and constitute more than 95% of the diabetes population [2] [3] [4]. The chronic hyperglycemia associated with disturbance in fat and protein metabolism, if not treated adequately can lead to long term vascular complications as well as acute metabolic complications, susceptibility to infection and non-alcoholic fatty liver disease [5] [6] [7] [8].

Diabetes related vascular complications can be broadly classified as Microvascular complications which affect retina (Diabetic retinopathy), kidney (Diabetic nephropathy) and the peripheral nerves (Diabetic neuropathy) or macrovascular complications which includes coronary artery disease, cerebrovascular disease and peripheral vascular disease. Premature morbidity and mortality in diabetes occurs due to these complications. Diabetic nephropathy is the leading cause of End Stage Renal Disease (ESRD) worldwide [5].

Early work for diabetic renal disease in India was done under the aegis of World Health Organisation (WHO) in 1975 to 1978. In this Multi National Study of Diabetic Vascular Disease (M.N.S.D.V.D) spanning fourteen countries with India as one of the centres (Delhi) observed DN in 9.3% males and 4.2% females with DM duration of 0 - 6 years, in 10.7% males and 5.7% females with DM duration of 6 to 13years and in 23% males and 13.6% females with DM duration of ≥14 years [9]. Data presented in **Table 1**.

Significant albuminuria or serum creatinine >1.5 mg/dl.

Following the same method Indian Council of Medical Research (ICMR) conducted a study in nine centres in India in which SCB Medical College & Hospital, Cuttack was one of the centre. DN in this study was observed in 12.2% of males and 5.3% of females in the first group (DM duration of 0 - 6 years), in 18% males and 8.7% females in the second group (DM duration of 6 - 13 years) and in 22.5% males and 7.5% of females in the third group (DM duration ≥ 14

Table 1. Diabetes renal disease [9].

W.H.O.M.N.S.V.D. (1975-78)				ICMR (1986-89)			
14 Countries				9 Centres			
(Delhi Centre)							
Duration (Yrs)	0-6	7 - 13	≥4	Duration (yrs)	0 - 6	7 - 13	≥14
M(n-289)	9.3	10.7	23.0	M (n = 262)	12.2	18.0	22.5
F(n-266)	4.2	5.7	13.6	F (n = 245)	5.3	8.7	7.5

Table 2. Mortality data. AIIMS—causes of death (percent) amongst diabetics in the last 3 decades [9].

Cause of Death	1966	1976	1986
	n = 75	N = 560	n = 580
DKA	9.3	12.4	6.5
Total Vascular Disease	76.0	69.0	74.5
Cardiac	42.3	29.1	23.8
Cereberal	11.0	11.7	10.5
Renal	22.7	28.2	40.2
Cirrhosis	6.7	3.2	3.3
Infections	2.7	5.5	9.2
Others	4.0	9.9	6.5

years) [9]. Another study in All India Institute of Medical Sciences (AIIMS), Delhi analysed the mortality amongst diabetics from 1966-86 (three decades) and observed that death due to renal cause was 22.7% in 1966, 28.2% in 1976 and 40.2% in 1986 respectively [9]. Data presented in **Table 2**. A study from Cuttack has revealed DN as the cause of death in 17% and 35% of cases in T2DM patients in 1977 and 1988 respectively [6]. Nephropathy affects 20-30% of T2DM patients according to western studies [10].

Pioneering epidemiological work done by Indian CKD Registry established under the aegis of Indian Society of Nephrology(ISN) had made pertinent observations that diabetes mellitus is the cause of CKD in 31.2% of patients [11]. Screening and Early Evaluation of Kidney Disease (SEEK) study reported prevalence of CKD to be 17.4% (urban 25.5% vs rural 9.4%).

Study in Cuttack showed that there was greater degree of insulin resistance and β cell dysfunction and atherosclerosis in diabetics than non-diabetics with chronic kidney disease [12]. Another study from the same institute has revealed that proteinuria is common and more related to glycemic status. Microalbuminuria in Type-2DM patients found to be a marker of generalised vascular endothelial dysfunction in the same study [12]. Indian Council of Medical Research (ICMR) study had revealed nephropathy in 15.4% males and 13.9% of females [13].

The Chennai Urban Rural Epidemiological Study (CURE) revealed overt proteinuria in 2.2% and microalbuminuria in 26.9% of population [14]. The Chunampet Rural Diabetes Prevention Project (CRDPP) study revealed the prevalence of diabetic nephropathy to be 24.3% [3]. Study from Bikaner and North Delhi (Clinic Based) revealed the prevalence of diabetic nephropathy to be 26.8% and 15.3% respectively [7] [8]. According to CINDI study (Multicentric Clinic Based), the prevalence of diabetic nephropathy in newly detected diabetes mellitus is 13.15% [15].

Till date there are few studies regarding different types of nephropathy in patients of Type-2 Diabetes Mellitus. Hence the present study was conducted to evaluate renal involvement in patients of Type-2 diabetes mellitus.

2. Aim of the Study

This study was carried out to determine various renal histopathological lesions in Type-2 diabetis mellitus patients with renal dysfunction and to establish clinicpathological correlation.

3. Materials and Methods

Hundred (100) Type-2 DM patients consecutively admitted to PG Department of Medicine of S.C.B. Medical College and Hospital, Cuttack were evaluated for presence of nephropathy. Out of hundred (100) consecutive Type-2 DM patients 32 cases were found to have nephropathy as per the inclusive criteria of macrolabuminuria (>300 mg/dl) and/or serum creatinine > 1.2 mg/dl [5]. They were enrolled for the study, out of which 20 were males and 12 were females. The study had Institute Ethical Committee (IEC) approval.

All T2DM patients with nephropathy of both genders having age more than 30 year were included in the study while patients with Type 1 Diabetes, Gestational Diabetes, Secondary Diabetes, patients with HIV infection, patients on steroid therapy, patients on chronic use of nephrotoxic drugs, solitary kidney on ultrasound of abdomen and pelvis, deranged coagulation profile, thrombocytopenia, uncontrolled hypertension, urinary tract infection and obstructive uropathy were excluded from the study.

Detail clinical evaluation was done in all cases. Laboratory investigation like complete blood count (CBC), urine routine and microscopic, urine culture, fasting blood glucose, 2hr postprandial blood glucose, HbA1c, serum urea and creatinine, 24 hour urinary protein, serum sodium and potassium, liver function test, lipid profile, ECG and ultrasound of abdomen and pelvis were done after obtaining fully informed written consent.

Renal biopsy was done by nephrologist in the department of nephrology after recieving proper consent from the patients in S.C.B. Medical College Hospital, Cuttack. Kidney biopsy was performed with real-time ultrasound guidance and disposable automated biopsy needles. We used 18-gauge needles for greater tissue yield and fewer bleeding complications.

The tissue core was examined under light microscope to ensure that renal cortex had been obtained. A second pass of the needle was usually performed to obtain additional tissue where ever needed.

Histopathological study was done in Department of Pathology, S.C.B. Medical College, Cuttack. The renal tissue was placed in formalin and 3 μm thin, uniform cut sections were used for light microscopy. 10% aqueous formaldehyde buffer solution was used for fixation for light microscopy. The specimen was stained with hematoxylin and eosin (H&E), periodic acid–Schiff (PAS) and silver methenamine.

Diabetic nephropathy has been classified into 4 stages based on biopsy studies which are:

Class I	Glomerular basement membrane thickening, mild nonspecific changes by light microscopy
Class IIa	Mild mesangial expansion
Class IIb	Severe mesangial expansion but without nodular sclerosis
Class III	Nodular sclerosis
Class IV	Advanced diabetic glomerulosclerosis, more than 50% of glomerulosclerosis.

The data were analyzed using SPSS version 18. For continuous variables, data were presented as the mean ± standard deviation or the median with range, and the means were compared using one-way analysis of variance. For categorical variables, the data were presented as counts and percentages, and the differences were analyzed using the Chi-square test.

4. Results

Thirty two patients (32) with diabetic nephropathy (20 males and 12 females) formed the study group out of hundred (100) Type-2 diabetes mellitus patients (58 males and 42 females) screened. Thus, the frequency of occurrence of clinical diabetic nephropathy was 32%. Majority of patients were from the age group of 50 - 60 years (56.25%).Most of the patients were having duration of diabetes of 6 - 10 years (87.5%). Positive family history of diabetes was present in 37.5% of patients (35% among males and 41.66% among females).Most cases of DN (Diabetic Nephropathy) presented with pedal edema as evidenced by 31 (96.87%) of patients including 19 (59.37%) males and 12 (37.50%) females had this finding. The mean BMI in the study group was 23.96 ± 1.93. Hypertension was present among 28 (87.50%) of patients including 19 (59.37%) males and 9 (28.12%) females. The mean SBP in our study group was 155 ± 10.31 mmHg and the mean diastolic blood pressure (DBP) was 88.25 ± 6.88 mmHg. The mean GFR and HbA1c in our study population were 41.64 ± 19.78 mL/min and 8.53 ± 1.18 respectively.

Among risk factors hypertension was present in 87.5%, dyslipidemia in 78.125% and smoking history in 43.75% of cases respectively.

Results of multiple linear regression analysis showed that duration of diabetes and HbA1C levels are strongly associated with development of nephropathy (p value < 0.05 for each) in diabetes.

Histopathological findings: Out of thirty two diabetic nephropathy patients, sixteen cases gave consent for renal biopsy. The histopathological findings were summarised in Table 3 and presented in Figures 1-3.

4.1. Glomerular Lesions

a) Glomerular Obsolescence (global sclerosis): 12(75%) of the patients had biopsy specimen with varying degrees of glomerular obsolescence (global sclerosis).

Table 3. ABLE.1 Histopathology of renal biopsy.

Histopathological lesion	No of cases (16)	Total (100%)
Global sclerosis	12	75%
Diffuse glomerulosclerosis	15	93.75%
Nodular glomerulosclerosis	10	62.5%
Membranous glomerulopathy	3	18.75%
Focal necrotising glomerulonephritis	1	6.25%
Tubular atrophy	14	87.5%
Vacuolation	10	62.5%
Casts	15	93.75%
Interstitial fibrosis	14	87.5%
Hyaline change	14	87.5%
Intimal thickening	12	75.00%

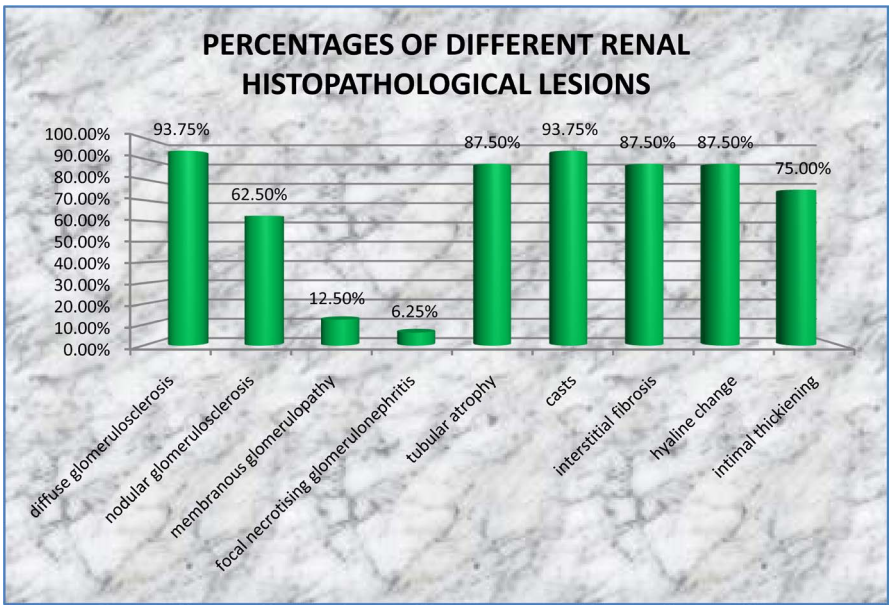

Figure 1. Different histopathological lesions in Kidney biopsy of Type-2DM patients with neprhopathy.

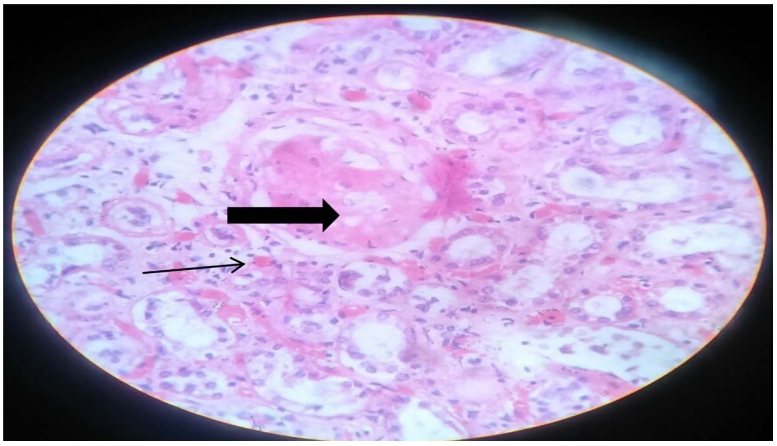

Figure 2. Renal biopsy from a 63 year old Type-2DM patient showing globally sclerosed glomeruli (thick black arrow) and arteriolar hyalinosis (thin black arrow).

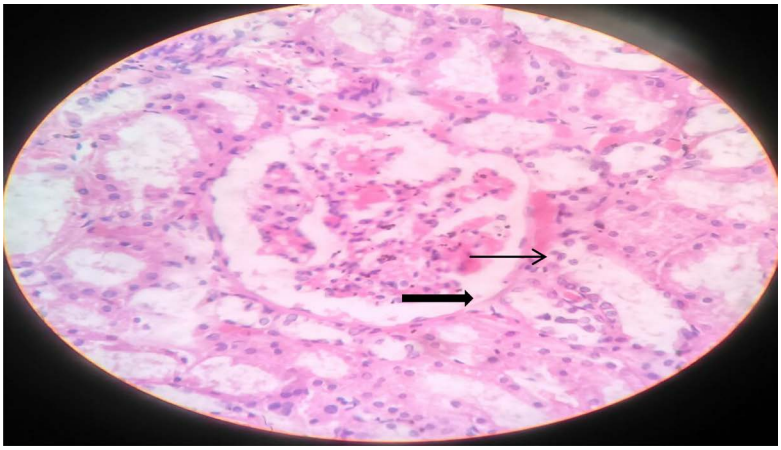

Figure 3. Renal biopsy from a 68 year old male Type-2 DM patient showing nodular glomerulosclerosis (thick black arrow) and basement membrane thickening (thin black arrow).

b) Diffuse glomerulosclerosis (DGS): Diffuse glomerulosclerosis was the most common form of glomerular lesion seen. It was present in 15 (93.75%) patients (13 males and 2 females).

c) Nodular glomerulosclerosis (NGS): Nodular glomerulosclerosis was seen in 10 (62.50%) patients (8 males and 2 females).

d) Non diabetic nephropathy was found in 3 biopsy (18.75%) of which 2 (12.5%) were membranous glomerulopathy (MGN) with evidence of segmental tuft sclerosis in 9/35 (25.70%) of the sampled glomeruli in one patient and 1/9 (11.11%) in another patient; and 1 (6.25%) was focal necrotising glomerulonephritis, with partial fibrocellular crescents over 4/26 (15.30%) glomeruli.

4.2. Tubular Lesion

Tubules showed focally prominent cytoplasmic vacuolar change. 10 biopsies (62.50%) showed tubular vacuolaton. 14 (87.50%) cases showed tubular atrophy with varying severity. Varying degrees of hyaline and granular casts were ob-

served in tubules. Casts were present in 15 (93.75%) of cases.

4.3. Interstitial Fibrosis

14 (87.50%) patients had interstitial fibrosis of varying severity with interstitial inflammation.

4.4. Vascular Lesion

Arterioles showed intimal thickening in 12 (75%) cases and hyalinosis in 14 (87.50%) of patients.

The difference in the clinical manifestations between between Diffuse Glomerulosclerosis and Nodular Glomerulosclerosis is presented in Table 4 and the biochemical parameters are given in Table 5. There was no statistical difference in age, duration of diabetes, BMI as well as syostolic and diastolic blood pressures in both the groups. The gender distribution was also comparable.

As presented in Table 5, the mean HbA1C was more than 9% in both the groups. The creatine clearence was around 30 ml/min and was similar in both the groups. Proteinuria of more than 1500 mg/day was observed in both the

Table 4. Clinical data of patients undergone kidney biopsy and diagnosed to be cases DGS and NGS.

	Diffuse glomerulosclerosis	Nodular glomerulosclerosis	p-value
No of cases	15	10	
Age(years)	59.4 ± 8.67	59.6 ± 9.33	0.9567
Sex(M/f)	13/2	8/2	1.000
Duration of diabetes (years)	9.4 ± 1.95	9.7 ± 2.26	0.7267
BMI(kg/m^2)	24.26 ± 2.60	23.73 ± 2.39	0.6113
SBP(mm/Hg)	158.4 ± 7.79	159.80 ± 8.61	0.6767
DBP(mmHg)	87.33 ± 5.27	87.00 ± 6.34	0.8887

Table 5. Biochemical-pathological correlation.

	Diffuse glomerulosclerosis	Nodular glomerulosclerosis	p-value
HBA1c	9.08 ± 1.18	9.21 ± 1.19	0.7904
Creatinine clearance (ml/min)	34.83 ± 17.45	35.649 ± 19.81	0.9142
Serum urea	81.46 ± 42.42	81.70 ± 51.44	0.989
Creatinine (mg/dl)	2.56 ± 1.004	2.64 ± 1.173	0.8567
24 hour urinary protein (mg/day)	1504 ± 470.81	1586 ± 545.20	0.692
Serum triglycerides	145.00 ± 36.05	143.80 ± 29.08	0.931
Total cholesterol	205.53 ± 68.16	219.70 ± 60.28	0.599
LDL cholesterol	93.00 ± 20.18	95.30 ± 23.07	0.794
HDL cholesterol	45.86 ± 10.23	44.50 ± 11.28	0.757

groups. Serum cholesterol levels were higher but mean value of LDLc was below 100 mg/dl where as HDLc levels were above 40 mg/dl in both the groups.

5. Disscussion

Diabetes mellitus is the commonest metabolic disorder and has a high prevalence in India [8]. Diabetic nephropathy is a clinical hall mark of microangiopathy and is the most important single disorder leading to renal failure in adults [4].

Till date, scanty studies have been conducted regarding the type of nephropathy in T2DM in this part of India, hence this study was conducted to evaluate nephropathy with histopathological changes in T2DM patients.

We found the incidence of diabetic nephropathy to be 32% in hospitalised patients. It has been reported that among 4837 patients with chronic renal failure seen over a period of 10 years, the prevalence of diabetic nephropathy was 30.3% India [16]. Other studies have shown prevalence of nephropathy to be 24.3% in Tamilnadu by CRDPP study [3] and 30.2% in Bikaner respectively and a cross-sectional study from Lucknow in 2012 showed prevalence of diabetic nephropathy to be 20% [17].

Another study from Karnataka by Raja Reddy *et al.* [18] in 2012 had reported the prevalence of diabetic nephropathy as 37.02% (Microalbuminuria was 30.79% in males and 24.46% in females and overt nephropathy was 9.27% in males and 6.73% in females).

The mean duration of diabetes was 8.25 ± 1.98 years in our study. Similar study by Rudberg *et al.*, in a study of adolescents with a mean duration of disease of 10.9 years, found that the duration of disease was an important factor in the overall severity of glomerulopathy [19].

The duration of diabetes, HbA1c level, Systolic and diastolic blood pressure and serum creatinine values are higher in NGS compared to the DGS variety. But there was no statistically significant difference between clinical and biochemical parameters in patients with nodular glomerulosclerosis and diffuse glomerulosclerosis.

The mean duration of diabetes was below 10 yr where as the mean age of patients was below 60 yrs suggesting development of nephropathy occurring at much earlier age in the T2DM in India than described in western literature [5].

The cohurt under study and mean BMI below 25 suggested that obesity is not a deciding factor in T2DM suffering from nephropathy in our population.

Even though majority of patients are in chronic kidney disease stage 3 (CKD stage 3) as per Cr. Clearance the biochemical parameters were worse than expected. (mean Creatinine above 2.5 mg% and serum urea above 80 mg%). This is an observation which is different from that observed in standard literature. The dyslipidemia observed neither revealed low HDLc nor high triglyceride which is classically seen in Indian diabetes. The most important risk factor for development of nephropathy was duration of diabetes followed by hypertension and

smoking. The CURES-45 reported that risk factors for overt diabetic nephropathy include HBA1C, duration of diabetes, and systolic blood pressure, while for microalbuminuria smoking and diastolic blood pressure were also risk factors [14].

Multiple linear regression analysis of various risk factors with diabetic nephropathy is presented in **Table 6**. In our study the duration of diabetes, HbA1c, serum urea and HDL cholesterol were strongly associated with development of diabetic nephropathy (p value of <0.05 for each). Similar type of study with regression analysis of risk factors by Agrawal *et al.* in 2012 from Bikaner, Rajasthan reported that duration of diabetes and HbA1c were strongly associated with diabetic nephropathy [17].

Histopathologically, DGS was the most predominant form of renal abnormality found in 93.75% followed by NGS in 62.50%, membranous nephropathy in 12.5% and focal necrotising glomerulonephritis in 6.25% of cases respectively. Study by Olsen *et al.* on 33 biopsies showed that 4 (12.12%) had Non Diabetic Renal Diseases (NDRD) and remaining 29 (87.87%) patients had DGS (9 = 27.27%) and NGS (20 = 60.60%) [20]. Another study by Prakash J. *et al.* showed prevalence of NDRD in diabetes to be 12.3%. at par with our study [21]. A study by Mathur *et al.* (1964) showed 71.9% of DN had DGS and 6.2% had combined DGS and NGS [22].

M Sahay *et al.* reported 24.56% NDRD and 75.43% DN [23]. DGS and NGS are the two predominant histopathological changes in DN according to western data [24]. Another study by Hirose showed diffuse and nodular lesions in 77.5%

Table 6. Results of multiple linear regression analysis showing association of various risk factors with diabetic nephropathy dependent variable (24 hour urinary protein).

Variable	Regression coefficient β	P value	95% Cl Of coefficient of β
Age	0.151	0.326	−12.199 - 34.625
Duration of DM	0.611	0.013	39.409 - 288.190
SBP	−0.232	0.306	−0,35.879 - 11.937
DBP	0.017	0.901	−20.760 - 23.391
FBS	−0.029	0.898	−7.052 - 6.231
HbA1c	0.656	0.026	39.824 - 548.531
Serum urea	−0.609	0.035	−18.045 - 0.752
Serum creatinine	−0.270	0.926	−190.965 - 174.681
GFR	0.008	0.977	−15.370 - 15.799
BMI	−0.281	0.070	−161.289 - 6.999
CHOL	−0.052	0.728	−3.366 - 2.400
TG	−0.183	0.353	−7.721 - 2.910
HDL	0.327	0.039	1.127 - 39.302
LDL	0.140	0.432	−8.077 - 18.023
VLDL	−0.293	0.088	−40.086 - 3.067

and 21.7% respectively [25]. The findings in our study are comparable to those of earlier studies.

There was not much difference between the clinical and biochemical parameters between patient of DGS and NGS. Similar study by Schwartz *et al.* in 1998 observed little difference between the clinical and biochemical parameters in these two types of DN patients [26].

6. Conclusions

Nephopathy occurs at a much earlier age in T2DM patients in India and the duration of diabetes resulting in nephropathy is less as compared to the western population. The typically described high triglyceride and low HDLc in Indian diabetics were not found in our study.

We conclude that nephropathy in patients of T2DM mellitus is of two distinctive pattern of glomerular pathology *i.e.* DGS and NGS. There was little difference between clinical and biochemical parameters in the DGS and NGS groups with respect to age, hypertension, BMI, duration of diabetes, dyslipidemia and glycemic control as reflected by HbA1c levels. Also noteworthy in the findings of this study was the fact that glomerular lesions other than those associated with diabetes were found in only three (3) patients. Hence, coexisting non diabetic renal disease may be associated with diabetic nephropathy in only a few patients with T2DM. Studies evaluating renal Parenchymal changes in T2DM are limited. Larger studies undertaking Histopathological evaluation of T2DM with Nephropathy will throw more light on NDRD & DN.

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