Original Article

A study of modifiable and non-modifiable risk factors associated with of diabetic nephropathy - A preliminary observational study in Eastern Odisha, India

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Abstract

Background: One of the commonest complications of poorly controlled Type 2 diabetes mellitus (T2DM) is Diabetic nephropathy (DN), which occurs in 30-40% of DM cases. It is important to identify the high-risk group who are likely to develop DN with the modifiable and non-modifiable risk factors. This study had the objectives to estimate and correlate the levels of the urine albumin creatinine ratio (UACR) with age, anthropometric measures, glycaemic control markers, lipids and renal function. To estimate each variable as independent and multivariate risk factors.
Materials and Methods: It was an observational and cross-sectional study conducted in a tertiary care centre in Eastern India. Totally, 221 consecutive ambulatory T2DM subjects were recruited after obtaining their written consent.
Results: The diabetics were classified as having diabetic nephropathy by the urine albumin creatinine ratio (ACR) of >30 mg/gm. 53.4% of our study group had DN. There was a significant risk associated with PPBS with p=0.043 (<0.05), serum creatinine with p=0.032 (<0.05), and urine albumin with p=0.0001 (<0.001). The multivariate regression analysis of all these variables there was a highly significant likelihood ratio for predicting DN with p=0.0001 (<0.001) with a predictive value of 74.5% in females and 75% in males.
Conclusion: The additive factors contributed by the risk factors in prediction of DN will benefit the DM in prevention of DN.

Key words: diabetic nephropathy, risk factors, diabetic kidney disease, Asian Indian

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Introduction

Diabetic nephropathy (DN) affects approximately 40% of the type 2 diabetes mellitus (T2DM) patients. [1] DN is diagnosed by the presence of albumin in urine. They are classified as microalbuminuria and macroalbuminuria with urine albumin: creatinine ratio of 30 - 300 mg/gm in the former and > 300 mg/gm in the latter. Microalbuminuria stage of renal involvement was termed as incipient nephropathy which may already be present in T2DM at the time of diagnosis. [2] Progression of normo-albuminuria to micro and macroalbuminuria can occur silently and faster with associated risk factors like dyslipidaemia, smoking habit, hypertension and poor glycaemic control. [3] In the South-Asian population, there is an increased predisposition to DN irrespective of the central obesity, [4] hence the need to point causal factors to body fat distribution initiating insulin resistance and inflammation. In routine management of diabetic patients, their blood and urine tests are done annually to monitor the disease control and to screen for DN. Microalbuminuria is also associated with increased risk for cardiovascular diseases and death. [1] Hence, it is imperative to adopt strategies for preventing the development of microalbuminuria and in delaying the progression to advanced stages of DN. That can be achieved by good glycaemic control by maintaining glycated haemoglobin (HbA_1C) at 7%, treating comorbidities like hypertension and dyslipidaemia.

Though microalbuminuria is the gold standard for screening and detection of DN, its determination in clinical laboratories are inconsistent because of the immunoassay techniques used [5, 6]. In diabetics, the albumin in urine can be modified by non- enzymatic glycation and

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hydrolysis during its passage in the renal tubules. These modifications can underestimate the albumin by the antibodies used for assay [7, 8], thereby delay the detection of DN and its treatment. In this study we assessed the correlation of ACR with non-modifiable risk factors like age and gender of patient and with modifiable risk factors like body mass index (BMI), waist hip ratio (WHR), atherogenic index (AI) calculated from fasting blood lipid levels and HbA_1C.

Material and Methods:

It was a cross-sectional comparative study on 221 ambulatory T2DM subjects conducted in a tertiary care centre in Eastern India after the approval of the Institutional Ethical Committee (IEC- T/IMF/18-19/32). The cases were from our Non – Communicable Diseases (NCD) Out-patients clinic (OPD), All India Institute of Medical Sciences, Bhubaneswar, India, who attended for routine follow-up clinic during the month of March 2020. Convenient sampling was done due to the COVID-19 pandemic. Their clinical and anthropometric data were noted after obtaining their written consent. 5ml of blood in fasting state and 10 ml of midstream spot urine was collected in different vacutainers and urine vials for estimation of the following: serum creatinine, glycated haemoglobin fasting (FBS) and post prandial blood sugar (PPBS), urine creatinine and albumin. The lipid profile included total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) and low-density lipoproteins (LDL). All the estimations were done the same day using the Beckman Coulter Chemistry Analyzer AU5800 (Beckman Coulter, Brea, USA).

The calculated parameters were body mass index (BMI), waist hip ratio (WHR), atherogenic index of plasma (AIP) [9], urinary albumin: creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR). [10] The statistical analysis was done to compare the diabetics with and without DN. The comparison was done by Mann Whitney U test.

The relative risk estimates were calculated and the correlation was estimated for the independent variables by Spearman's correlation as the data were not normally distributed which was seen by the Kolmogorov-Smirnov test. The comparisons between gender groups and those with and without DN were by Kruskal Wallis Test and post hoc test by Tukey's test. The multivariate regression was estimated for the independent variables. All these were done using SPSS 19.0 version [IBM, Armonk, NY, USA]. p-value <0.05 was considered as statistically significant.

Results:

Clinical characteristics: There were 221 diabetic patients who consented to participate in the study. There were 143 males and 78 females. **Table-1** shows the general clinical characteristics of the study participants. Considering the anthropometric cut-off levels for Asian Indians, 72.4% were overweight and obese; 94.4 % of males and 98.7 % females had high WHR. 79.1% had poor glycaemic control as seen by HbA_1C and 90.9% had a high-risk dyslipidaemia as seen by the AIP. Though 53.4 % of our study group had DN, a larger proportion of the total that is 72.8% had decreased eGFR. The study participants were classified as having diabetic nephropathy by the UACR.

Table 1: Distribution of general characteristics of the study population (N=221)

Covariates		No. of Patients	Percentage
Age (in years)	< 60	172	77.8
	≥ 60	49	22.2
Gender	Male	143	64.7
	Female	78	35.3
BMI	<23	61	27.6
	≥23	160	72.4
WHR	M, <0.90	8	5.6
	M ≥0.90	135	94.4
	F < 0.80	1	1.3
	F ≥0.80	77	98.7
HbA_1C	<7.0%	46	20.8
	≥7.0%	175	79.1
AIP	<0.24	20	9.1
	≥0.24	201	90.9
ACR	< 30 mg/gm	94	42.5
	≥ 30 mg/gm	127	57.5
eGFR	> 90 ml/min	60	27.2
	< 90ml/min	161	72.8
DN	Absent	103	46.6
	Present	118	53.4

The comparison of the two groups by Mann Whitney U test. There was a significant difference in PPBS (p=0.013), HbA_1C (p=0.041) and UACR (p<0.001). There was no significant difference in the age, gender, BMI, WHR, FBS, lipid profile, AIP, serum creatinine and eGFR between the groups as shown in **Table-2**.

Association of risk factors with DN:

The risk estimate calculated using the cut off values for each variable relevant to our population and as per gender wherever applicable. Though there was a 10–20% increased risk for age >60 years, male gender, BMI, WHR, FBS, HbA_1C, AIP and LDL among the serum lipids and a 20% decrease in HDL had increased risk of DN, none were statistically significant as shown in **Table-3**.

This may be because of the consecutive convenient sampling of one month evaluated as a preliminary study here. There was a significant risk associated with PPBS (p=0.043), serum creatinine (p=0.032), and urine albumin (p=0.0001).

Table 2: Differences Between Diabetic Nephropathy Group for Various Risk Factors

Parameters		Diabetic Nephropathy		p value
		Absent (n = 94)	Present (n = 127)	
Age		52 (43 – 60)	50 (43 – 58)	0.636
Sex	Male	62 (65.96%)	76 (59.84%)	0.353
	Female	32 (34.04%)	51 (40.16%)	
BMI (kg/m^2)		25.30 (23.46 – 27.69)	25.34 (22.22 – 28.06)	0.434
WHR		0.948 (0.91 – 0.99)	0.946 (0.91 – 0.98)	0.439
FBS (mg/dl)		141.5 (121 – 179)	152 (122 – 221)	0.187
PPBS (mg/dl)		208.5 (185 – 290)	245 (189 – 321)	**0.013**
HbA$_1$C (%)		7.875 (7.08 – 8.8)	8.3 (7.2 – 10.3)	**0.041**
S. Creatinine (mg/dl)		1 (0.8 – 1.1)	1 (0.8 – 1.2)	0.393
eGFR (ml/min)		82.53 (66.67 – 94.31)	74.77 (64.94 – 91.08)	0.142
TC (mg/dl)		187 (161 – 210)	190 (159 – 227)	0.613
TG (mg/dl)		153 (119 – 204)	149 (108 – 204)	0.648
HDL (mg/dl)		44 (38 – 51)	46 (39 – 53)	0.160
LDL (mg/dl)		110 (91 – 135)	114 (92 – 136)	0.740
AIP		0.557 (0.43 – 0.69)	0.529 (0.37 – 0.69)	0.280
UACR (mg/gm)		14.41 (6.53 – 22.23)	82.5 (46.95 – 190.43)	**<0.001**

Bolded p-value < 0.05 Statistically Significant

The Spearman's correlation (**Table 4**) of ACR with FBS, PPBS, HbA$_1$C and u. albumin were positive with (p=0.028, <0.001, 0.001 and <0.001 respectively) on overall estimation of all cases (not shown here). But on estimating the correlation in females, only PPBS correlated significantly and in males there was significant positive correlation with FBS, PPBS, HbA$_1$C, serum creatinine and spot urine albumin was negative with eGFR with p=0.028. The other individual independent factors like age, BMI, WHR, serum lipids and AIP did not correlate significantly with ACR in both sexes. On doing a multivariate logistic regression analysis of all these variables **[Table 5a and 5b]** there was a significant likelihood ratio for predicting DN (p=0.014 and 0.001 in females and males respectively) with a substantial predictive value of 74.5% in females and 75% in males by Cox and Snell R square.

Discussion:

Diabetic nephropathy is a common complication of T2DM. It is usually detected in late stages from where it rapidly progresses to end stage renal disease (ESRD). Early detection, good glycaemic control and nephro-protective treatment can prevent ESRD. [11] Apart from this it is important to identify the subgroup among T2DM, likely to develop DN considering the modifiable risk factors like body fat, serum lipids, kidney function and glycaemic control. From our preliminary it is evident that there is a risk associated with biomarkers of glycaemic

Table 3: Risk Factors (Modifiable & Non-Modifiable) for Diabetic Nephropathy

Factors	Parameters	Classifications	Diabetic Nephropathy		Relative Risk	P Value
			Absent	Present		
Non - Modifiable	Age (in years)	<60	74	108	1.218	0.284
		≥60	20	19		
	Sex	Male	62	76	1.165	0.400
		Female	32	51		
Modifiable	BMI (kg/m^2)	<23	20	41	1.250	**0.048**
		≥23	74	86		
	WHR	<0.9(M)/<0.85 (F	1	1	1.177	1.000
		≥0.9(M)/ ≥0.85(F)	93	126		
	FBS (mg/dl)	<110	9	22	1.284	0.119
		≥110	85	105		
	PPBS (mg/dl)	<140	3	0	2.396	**0.043**
		≥140	91	127		
	HbA$_1$C (%)	<7	23	23	1.232	0.315
		≥7	71	104		
	Serum Creatinine (mg/dl)	≤1.2(M)/ ≤1.1(F)	87	105	1.877	**0.032**
		>1.2(M)/>1.1(F)	7	22		
	eGFR (ml/min)	<90	67	94	1.062	0.650
		≥90	27	33		
	TC (mg/dl)	<200	60	80	1.021	1.000
		≥200	34	47		
	TG (mg/dl)	<150	44	65	1.077	0.587
		≥150	50	62		
	HDL (mg/dl)	>35(M)/>39(F)	77	112	0.767	0.246
		<35(M)/<39(F)	17	15		
	LDL (mg/dl)	<100	36	42	1.138	0.477
		≥100	58	85		
	AIP	≤0.24	6	14	1.245	0.343
		>0.24	88	113		
	Urine Albumin (mg/L)	<30	70	33	3.341	**0.0001**

Bolded p-value < 0.05 Statistically Significant

control (PPBS and HbA$_1$C), more so in males as compared to females. Similar results have been reported by authors in Asia [12] among Asians in Europe [4], and from heterogenous populations from 20 cohorts. [13] Though strict glycaemic control decreased the risk for DN b 40%, it alone cannot prevent the initiation and progression of DN. [1] Majority of our patients were overweight or obese and had higher WHR than normal. Though BMI associated significantly as a risk factor for DN with UACR, WHR didn't. Neither of them was different in the two groups. There was no difference in gender as a risk factor for DN. However, studies among Asians have shown that women who have DN rapidly progress to ESRD as compared to their male counterparts. [14, 15]

Table 4: Correlation of ACR with independent factors in the diabetics grouped according to gender (N=221)

Parameters	Females		Males	
	Spearman's rho	p value	Spearman's rho	p value
Age (years)	-0.137	0.228	0.032	0.703
BMI (kg/m^2)	0.05	0.661	-0.095	0.262
WHR	0.008	0.947	-0.083	0.329
FBS (mg/dl)	0.085	0.455	0.176*	**0.036**
PPBS (mg/dl)	0.267*	**0.017**	0.213*	**0.011**
HbA$_1$C (%)	0.161	0.156	0.248**	**0.003**
S. Creatinine (mg/dl)	0.076	0.508	0.191*	**0.022**
eGFR (ml/min)	0.043	0.705	-0.185*	**0.028**
TC (mg/dl)	0.172	0.129	-0.005	0.956
TG (mg/dl)	0.060	0.601	-0.070	0.406
HDL (mg/dl)	0.111	0.332	0.030	0.724
LDL (mg/dl)	0.176	0.120	-0.011	0.901
AIP	-0.015	0.895	-0.073	0.387
U. Albumin (mg/L)	0.752**	**0.001**	0.658**	**0.001**

**** Correlation is significant p<0.01; * Correlation is significant p<0.05**

Table 5a: Multivariate Regression of the independent variables as risk factors for DN

Model Fitting Information					
Sex	Model	Model Fitting Criteria	Likelihood Ratio Tests		
		-2 Log Likelihood	Chi-Square	df	Sig.
Female	Intercept Only	107.981			
	Final	0	107.981	78	**0.014**
Male	Intercept Only	196.741			
	Final	0	196.741	141	**0.001**

Bolded p-value < 0.05 Statistically Significant

Table 5b: Predictive value of the multivariate analysis

Pseudo R-Square		
Female	Cox and Snell	0.745
	Nagelkerke	1
	McFadden	1
Male	Cox and Snell	0.75
	Nagelkerke	1
	McFadden	1

The baseline eGFR and kidney function are important factors in DN risk and progression. [1] In our study though eGFR was not significantly different in the two groups; with and without DN, serum creatinine levels were a risk in both sexes and eGFR negatively correlated with UACR in males as shown in **Table-4.** As eGFR is closely related to age, baseline eGFR at the time of diagnosis of T2DM and further monitoring to see the rate of decline [16] is imperative for initiating treatment with antidiabetic agents which will protect the kidneys also. [12]

In our study, the serum lipids were not statistically different in the two groups, yet studies have shown that HDL and TG are independent risk factors for cardiovascular disease, systolic blood pressure (SBP) being the measure. [13] As we have not considered the treatment naïve T2DM patients and we have not taken in account the drug history of each participant, our statement for or against the association of serum lipids in DN will not be exact.

As T2DM involves multiple organs and its complications can coexist to varying degrees in individuals, multiple factors affect the course of the disease. The multivariate regression analysis showed significant predictive value of the risk factors considered in our study. Studies on identification of risk factors have identified similar factors and others like SBP, duration of disease, rate of decline in eGFR, age and presence of diabetic retinopathy. [3, 12]

The strength of our study is that, though it is a preliminary study conducted during the lockdown for pandemic, the conjoined effect of the modifiable and non-modifiable risk factors showed substantial predictive value. Our study is limited by the sample number and the lack of drug history such as lipid lowering agents, antihypertensives, insulin or oral hypoglycaemic agents.

Conclusion:

In conclusion, the findings of our study have implications in the clinical scenario of diabetes. As the disease, T2DM is not only about current glycaemic control, but involves constant clinical and lab monitoring to evade complications. Patient education about disease and empowering them with the knowledge and ability is more important that medications alone. An overall change in diet, physical activity, and other lifestyle modifications should benefit each patient. Larger cohort studies are suggested to understand the additive effects of risk factors.

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Authors' Contributions: SS, MT and SDM conceived the study design and initial draft of the manuscript. SD, SN and DSM collected clinical data. SS and SN analysed the data. All the authors edited and approved of the final draft of the manuscript.

Here, SS - Suchanda Sahu, MT - Manish Taywade, SD - Sujata Devi, SN - Saurav Nayak and, Dipti Sudha M - DSM

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Conflict of Interest: The authors declare that there was no conflict of interest.

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