

Risk factors for diabetic nephropathy among newly diagnosed type 2 diabetic patients with normal blood pressure

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ABSTRACT

Background: Patients with type 2 diabetes mellitus (T2DM) pass through pre-diabetic stages and during diagnosis, half of them may have different complications including diabetic nephropathy. Hypertension has adverse impacts on diabetic nephropathy. We aimed to evaluate the risk factors for diabetic nephropathy among newly detected T2DM patients with normal blood pressure.

Methods: A case-control study was done at a tertiary care hospital in Dhaka, Bangladesh from January 2018 to June 2019. Newly detected (<3 months), adult (≥ 18 years), T2DM patients, who underwent tests for urine albumin-to-creatinine ratio (UACR), at least twice, 6-weeks apart, were included in this study. Patients with hypertension, known kidney disease, features of glomerulonephritis, systemic diseases including systemic lupus erythematosus and vasculitis, history of recent fever and exercise, urinary tract infection and pregnancy were excluded. Patients with UACR ≥ 30 mg/g in at least two samples were cases and those with UACR < 30 mg/g were controls.

Results: Among the total 135 patients, 27 were cases [moderately increased proteinuria (previously, microalbuminuria) (UACR 30–299 mg/g) = 25 and severely increased proteinuria (previously, overt proteinuria) (UACR ≥ 300 mg/g) = 2] and 108 were controls. Multivariate logistic regression revealed that family history of diabetes (OR=2.13; 95% CI, 1.412 to 4.216, $p=0.003$) and diabetic nephropathy (OR=3.31; 95% CI, 2.145 to 5.249, $p=0.001$), smoking (OR=3.11; 95% CI, 2.234 to 4.123, $p=0.003$), dyslipidaemia (OR=2.14; 95% CI, 1.363 to 3.324, $p=0.005$) and diabetic retinopathy (OR=6.23; 95% CI, 4.197 to 9.464, $p=0.004$) were significant risk factors.

Conclusion: We concluded that, family history of diabetes and diabetic nephropathy, smoking, dyslipidaemia and diabetic retinopathy appeared as significant risk factors for diabetic nephropathy among newly diagnosed T2DM patients with normal blood pressure.

Key words: diabetic nephropathy, new, risk factors, type 2 diabetes mellitus.

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INTRODUCTION

The increasing prevalence of diabetes mellitus (DM) has become epidemic and this rise is mostly contributed by the increasing prevalence of type 2 DM (T2DM). Factors contributing to this rise of T2DM in susceptible individuals are mainly environmental and include rapid urbanization, physical inactivity, increasing body mass index (BMI) and occurring largely in low- and middle-income countries (LMICs).^{1,2} Chronic kidney disease (CKD) is a silent epidemic, having estimated global prevalence of

13.4%.³ DM is the leading cause of CKD and end-stage renal disease (ESRD), both in developed and developing countries.⁴ Diabetic nephropathy is one of the three classic micro-vascular complications of DM, traditionally described among patients with long duration and poor control of DM. Appearance of abnormal level of proteinuria, new onset hypertension, concomitant diabetic retinopathy and importantly, the absence of an alternative diagnosis for proteinuria are taken to make a diagnosis of diabetic nephropathy.⁵ Generally, all these are present in patients with known DM, either type 1 or T2DM but patients with T2DM pass through pre-diabetic stages, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) for a reasonable period before establishing the diagnosis and at the time of diagnosis, half of the T2DM patients may have different macro- and micro-vascular complications including diabetic nephropathy.⁶⁻⁸ Hypertension, itself, is an important cause of CKD. Hypertension may be a feature of diabetic nephropathy or it may be a separate entity but hypertension has been reported as a risk factor for diabetic nephropathy; whatever the way we explain, it is true that hypertension handles diabetic nephropathy adversely.^{9,10} Hypertension, itself, may cause proteinuria and kidney failure among patients without diabetes and antihypertensive medications, specially, angiotensin blocking agents can reduce proteinuria. Besides hypertension, other risk factors for diabetic nephropathy include obesity, smoking, abnormal lipids, presence of diabetic retinopathy, family history of diabetic nephropathy, etc.^{6,11,12} As hypertension can influence diabetic nephropathy adversely, it is important to identify other risk factors for diabetic nephropathy among normotensive patients. In this study, we evaluated the risk factors for diabetic nephropathy among newly detected T2DM patients with normal blood pressure.

METHODS

This case-control study was done at the out-patient department (OPD) of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine

and Metabolic Disorders (BIRDEM) General Hospital in Dhaka, Bangladesh from January 2018 to June 2019. Newly detected (duration of DM of 3 months or less since detection), adult (18 years or older), T2DM patients of either sex, who underwent tests for urine albumin-to-creatinine ratio (UACR), at least twice, six weeks apart (in a 6-month period), were included in this study. Patients with hypertension (newly diagnosed or known cases or on antihypertensive medications), diagnosed kidney disease, features of glomerulonephritis, systemic diseases including systemic lupus erythematosus and vasculitis, history of recent fever and exercise, urinary tract infection and pregnancy were excluded. Patients with UACR ≥ 30 mg/g in at least two (of three, if done) samples were cases⁵ and those with UACR < 30 mg/g were controls. Cases were divided in to moderately increased proteinuria (previously, microalbuminuria) (UACR 30 – 299 mg/g) and severely increased proteinuria (previously, overt proteinuria) (UACR ≥ 300 mg/g).⁵ The study protocol was approved by the Institutional Review Board (IRB) of BIRDEM General Hospital, Dhaka, Bangladesh. Data were collected from patients after taking informed written consents and were recorded in case record forms. Data were analyzed by Statistical Package for Social Sciences (SPSS) version 20. A p value of < 0.05 was taken as significant.

RESULTS

Total patients were 135, including 27 cases (moderately increased proteinuria = 25 and severely increased proteinuria = 2) and 108 controls. Mean age of the study participants was 42.9 years and there was female predominance (64.4%). Thirteen percent patients were smokers, 12% had dyslipidaemia, 51% had family history of DM and 45% had family history of diabetic nephropathy (Table I). Two patients had estimated glomerular filtration rate (sGFR) less than 60 ml/min/1.73 m² [chronic kidney disease-epidemiology (CKD-EPI) creatinine based equation].¹³ Diabetic retinopathy (6.7%) was the second most common chronic complication of DM (Table II).

Table I Base-line characteristics of study participants (N = 135)

Characteristics	Total = 135 frequency (%)	Cases = 27 frequency (%)	Controls = 108 frequency (%)	p value
Age (mean ± standard deviation), years	42.9±9.0	42.3±7.9	43.1±9.3	0.187
Male:	48 (35.6):	12 (44.4):	36 (33.3):	0.127
Female	87 (64.4)	15 (55.6)	72 (66.7)	
Positive family history of diabetes	69 (51.1)	18 (66.7)	51 (47.2)	0.005
Positive family history of diabetic nephropathy	31 (31/69, 44.9)	14 (14/18, 77.8)	17 (17/51, 33.3)	0.019
Past history of gestational diabetes mellitus	14 (14/87, 16.1)	4 (4/15, 26.7)	10 (10/72, 13.9)	0.003
Dyslipidaemia	16 (11.9)	3 (11.1)	13 (12.0)	0.738
Current smoker	18 (13.3)	7 (25.9)	11 (10.2)	0.003
Presentation of diabetes mellitus				
<i>Asymptomatic</i>	110 (81.5)	24 (88.9)	86 (79.6)	0.014
<i>Classical</i>	24 (17.8)	3 (11.1)	21 (10.4)	
<i>With complication</i>	1 (0.7)	-	1 (0.9)	
Glycaemic status				
<i>Fasting blood glucose (mmol/L)</i>	9.9±3.2	9.6±2.9	10.1±3.3	0.005
<i>2-h post-glucose value (mmol/L)</i>	16.6±3.9	15.3±3.0	16.9±4.1	0.003
<i>HbA1c (%)</i>	7.4±0.8	7.4±0.5	7.4±0.9	0.073
Estimated glomerular filtration rate (eGFR)¹³				
<i>≥90 ml/min/1.73 m²</i>	70 (51.9)	16 (59.3)	54 (50.0)	0.002
<i>60-89 ml/min/1.73 m²</i>	63 (46.7)	9 (33.3)	54 (50.0)	
<i>45-59 ml/min/1.73 m²</i>	2 (1.5)	2 (7.4)	-	

Table II Classical complications of diabetes mellitus among the study participants (N = 135)

Complications	Total = 135 frequency (%)	Cases = 27 frequency (%)	Controls = 108 frequency (%)	p value
Diabetic retinopathy	9 (6.7)	5 (18.5)	4 (3.7)	0.016
Diabetic peripheral neuropathy	1 (0.7)	-	1 (0.9)	-
Diabetic nephropathy	27 (20.0)	-	27 (100.0)	-
Coronary artery disease	2 (1.5)	-	2 (1.9)	-

On analyzing possible risk factors for diabetic nephropathy, univariate analysis revealed that, family history of diabetic nephropathy, smoking and coexisting diabetic retinopathy were significant (Table

III). On multivariate logistic regression, family history of DM and diabetic nephropathy, smoking, dyslipidaemia and diabetic retinopathy appeared as significant (Table IV).

Table III Univariate analysis of risk factors for diabetic nephropathy among the study participants (N=135)

Risk factors	Odds ratio (OR)	95% confidence interval (CI)	p value
Age	0.875	0.323 to 1.911	0.594
Sex	1.6	0.678 to 3.773	0.283
Smoker	3.086	1.066 to 8.934	0.037
Family history of diabetes mellitus	2.235	0.922 to 5.415	0.074
Family history of diabetic nephropathy	7.0	1.996 to 24.542	0.002
Dyslipidaemia	0.913	0.240 to 3.463	0.894
Presence of diabetic retinopathy	5.909	1.467 to 23.793	0.012
Body mass index	2.5	0.543 to 11.506	0.239
HbA1c	2.109	0.737 to 6.036	0.164

Table IV Multivariate analysis of risk factors for diabetic nephropathy among the study participants (N=135)

Risk factors	Odds ratio (OR)	95% confidence interval (CI)	p value
Age	0.457	0.313 to 0.812	0.357
Sex	0.532	0.213 to 1.134	0.531
Smoker	3.11	2.234 to 4.123	0.003
Family history of diabetes	2.13	1.412 to 4.216	0.003
Family history of diabetic nephropathy	3.31	2.145 to 5.249	0.001
Dyslipidaemia	2.14	1.363 to 3.324	0.005
Presence of diabetic retinopathy	6.23	4.197 to 9.464	0.004
Body mass index	0.204	0.019 to 0.549	0.003
HbA1c	0.132	0.108 to 0.543	0.002

DISCUSSION

Patients with T2DM pass undiagnosed for several years before detection and half of the T2DM patients remain undiagnosed.¹⁴ During this period of time, many of these T2DM patients develop different diabetic complications. In different studies, it has been seen that diabetic nephropathy reaches up to 50% or even more.^{6-8,15} If these complications are detected at an earlier opportunity and appropriate interventions including specific treatment and modification of risk factors can be instituted, an improved clinical outcome is expected. We evaluated risk factors for diabetic nephropathy among newly diagnosed T2DM patients with normal blood pressure in this study. We found family history

of DM and diabetic nephropathy, smoking, dyslipidaemia and concomitant diabetic retinopathy were significant risk factors for diabetic nephropathy among newly diagnosed, normotensive, T2DM patients.

Mean age of our patients was nearly 43 years and two-thirds were females. Mean age of new diabetic patients varied in different studies, depending upon geographic location and average life-expectancy of those countries. Martin et al reported over 51% of their newly detected diabetic patients were males with mean age of 46 years in Uganda¹⁶ while Sosale et al reported over two-thirds being males in India.¹⁷ Aboelnasr et al from Egypt reported two-thirds of newly detected diabetic patients

being females and mean age was over 48 years.⁶ Bansal et al reported female predominance of newly detected diabetic patients in another Indian report with mean age of nearly 50 years.¹⁸

Patients with T2DM and diabetic nephropathy have genetic influences.^{19,20} Our findings were no exception. Half of our patients had family history of DM and over 44% had family history of diabetic nephropathy. One-sixth of our female patients also had a past history of gestational diabetes mellitus. Mayega and Rutebemberwa from Uganda reported that over half of their newly diagnosed diabetic patients were females and one-fifth had a family history of DM.²¹

T2DM is a systemic disease. Increased BMI and dyslipidaemia are frequent associations. We found over four-fifths of our newly diagnosed T2DM patients were over-weight or obese and over one-tenth had dyslipidaemia. Dyslipidaemia appeared as a significant risk factor for diabetic nephropathy in our study which is in line of report by Aboelnasr et al from Egypt.⁶

Presence of diabetic retinopathy and proteinuria is almost diagnostic of diabetic nephropathy in type 1 diabetic patients. In T2DM patients, concomitant diabetic retinopathy is moderately sensitive⁵ but its presence almost certainly confirms the diagnosis of diabetic nephropathy. We found nearly 7% of our newly detected T2DM patients had diabetic retinopathy and diabetic retinopathy was a significant risk factor for diabetic nephropathy. This observation was in agreement with findings of several other reports.^{7,8}

Long duration and poor glycaemic controls are independent risk factors for diabetic complications including diabetic nephropathy. We included T2DM patients with duration of 3 months or less in our study. We are not sure for how long these patients were having abnormal glycaemic status. We did not find glycated haemoglobin (HbA1c) in our patients as a significant risk factor for diabetic nephropathy, which contradicts with findings of others.⁶ HbA1c is a reflection of previous 3 to 4 months glycaemic status, so the influence of short period of poor glycemic status, singly, may not be that much notorious, when it persists for years and is compounded with other risk factors including hypertension.

Hypertension is a recognized risk factor for diabetic nephropathy.⁶ Hypertension can cause CKD,

proteinuria, aggravate retinopathy and adversely influence the overall outcome. Antihypertensive medications reduce proteinuria and this effect is prominent for angiotensin converting enzyme inhibitors, angiotensin receptor blockers⁵ and non-dihydropyridine calcium channel blockers. We excluded hypertensive patients from our study considering it as a potential confounder.

Our research had some limitations. It was a single centre study on small number of study participants. This finding should not be generalized for all Bangladeshi newly diagnosed T2DM patients. On the other hand, the most strong point of the current research is that, we followed the standard recommended diagnostic criteria for diabetic nephropathy, contrary to some contemporary reports.^{7,16}

Conclusion

In conclusion, family history of DM and diabetic nephropathy, smoking, dyslipidaemia and concomitant diabetic retinopathy were significant risk factors for diabetic nephropathy among selected newly diagnosed Bangladeshi T2DM patients with normal blood pressure. We emphasize newly detected T2DM patients should be screened for complications including diabetic nephropathy during diagnosis and searched for potential modifiable risk factors and addressing these factors will ensure a better renal and patient outcome.

Authors' contribution: SZ and MAR planned the study, MAR collected data, SZ and MAR did literature search and drafted manuscript. SHH analyzed data. All authors read and approved the final manuscript for submission.

Conflicts of interest: Nothing to declare.

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