

# Risk Factors for Diabetic Nephropathy among Newly Detected Type 2 Diabetic Patients Attending a Tertiary Care Hospital of Bangladesh

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## Abstract:

**Background:** Patients with type 2 diabetes mellitus may present with different macro- and micro-vascular complications including diabetic nephropathy. This study was designed to evaluate the risk factors for diabetic nephropathy among newly detected type 2 diabetic patients.

**Methods:** This case-control study was done at BIRDEM General Hospital, Dhaka, Bangladesh from January to September 2017. Adult ( $\geq 18$  years), type 2 diabetic patients, who were detected as diabetic for the first time, within the previous three months and who tested, at least, 2 urine samples for urine albumin to creatinine ratio (UACR), at least 6 weeks apart, were consecutively enrolled for the study. Pregnant ladies, patients with diagnosed kidney disease, patients having features of glomerulonephritis and systemic diseases like vasculitis and systemic lupus erythematosus, history of recent fever, urinary tract infection and menstruation were excluded. Patients having UACR  $\geq 30$  mg/g in at least 2 (out of 3, if tested) samples were taken as cases and those with UACR  $< 30$  mg/g were controls. Data were analyzed by statistical package for social sciences (SPSS) version 20.

**Results:** Total patients were 224 with female predominance (150, 67%). Fifty one (22.8%) patients had diabetic

nephropathy (microalbuminuria = 47 and overt proteinuria = 4). Multivariate regression analysis revealed that, hypertension [odds ratio (OR) = 3.71; 95% CI 1.23 to 4.31,  $p = 0.003$ ], smoking (OR = 3.27; 95% CI 2.91 to 4.79,  $p = 0.003$ ), family history of diabetes (OR = 2.31; 95% CI 1.84 to 3.14,  $p = 0.005$ ) and diabetic nephropathy (OR = 3.34; 95% CI 2.40 to 4.97,  $p = 0.001$ ), dyslipidaemia (OR = 2.31; 95% CI 1.98 to 3.91,  $p = 0.023$ ), increased body mass index (BMI) (OR = 2.11; 95% CI 1.54 to 4.87,  $p = 0.001$ ) and high glycated haemoglobin (HbA1c) (OR 3.21; 95% CI 1.71 to 5.97,  $p = 0.034$ ) were significant risk factors for diabetic nephropathy.

**Conclusion:** One in every five type 2 diabetic patients had diabetic nephropathy during diabetes diagnosis and most patients had microalbuminuria. Hypertension, dyslipidaemia, smoking, family history of diabetes and diabetic nephropathy, increased BMI and high HbA1c were significant risk factors for diabetic nephropathy among newly detected type 2 diabetic patients.

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

(J Bangladesh Coll Phys Surg 2023; 41: 15-21)  
DOI: <https://doi.org/10.3329/jbcps.v41i1.63260>

## Introduction:

Diabetic nephropathy is one of the most common micro-vascular complications of diabetes mellitus (DM) and affects 20-40% of all diabetic patients.<sup>1</sup> Diabetic

nephropathy is typically described in patients with long duration of diabetes but patients with type 2 DM (T2DM) may present with diabetic nephropathy.<sup>2</sup> Diabetic nephropathy is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in developed countries and rapidly becoming the number one cause of CKD in developing countries, largely contributed by the increasing prevalence of T2DM.<sup>1,3-7</sup>

Over 90% of the global diabetic population are having T2DM and half of all T2DM patients remain undiagnosed.<sup>8</sup> T2DM typically passes through pre-diabetes stages before being identified. Because of such indolent course of T2DM, it is seen that when diagnosed, over half of T2DM patients have some form of diabetic complications.<sup>9-11</sup> In such patients, diabetic nephropathy ranges between 10 and 56.2% in different series.<sup>9-12</sup> In resource poor settings, patients may have

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Received: 16 June, 2022

Accepted: 25 Sept., 2022

less access to health care facilities and thus occurs delay in diabetes diagnosis.<sup>13</sup>

Risk factors for diabetic nephropathy include advanced age, obesity, long duration and poor control [high glycated haemoglobin (HbA1c)] of diabetes, presence of hypertension, dyslipidaemia, family history of diabetic nephropathy, presence of other microvascular diseases etc.<sup>14,15</sup> Among newly detected diabetic subjects, higher HbA1c levels, hypertension, increased age, dyslipidaemia and co-existing diabetic retinopathy are described as risk factors for microalbuminuria and overt proteinuria in different countries including India<sup>10,16,17</sup>, Pakistan<sup>11</sup>, Egypt<sup>2</sup>, Uganda<sup>18</sup> and Iran<sup>9</sup> but the exact prevalence of diabetic nephropathy and the predictors and/or associated risk factors are not well described among Bangladeshi patients with newly detected T2DM.

In resource constrain settings like Bangladesh, most newly detected T2DM patients undergo urine for routine and microscopic examinations, sometimes accompanied by semi-quantitative dipstick tests and serum creatinine levels for evaluation of kidney function. Microalbuminuria (24-hour urine albumin excretion between 30 and 299 mg) is the earliest sign of diabetic nephropathy, at which level dipstick test remains negative.<sup>19</sup> On the other hand, serum creatinine level may remain normal even in patients with nephrotic range proteinuria. So, it is assumed that large numbers of newly detected T2DM patients remain beyond proper evaluation for their renal status. These patients pass years after years without being properly evaluated unless they develop advanced stages of diabetic nephropathy and renal failure. With this context, this study was designed to evaluate risk factors for diabetic nephropathy among newly detected type 2 diabetic patients.

#### Methods:

A case-control study was done at outpatient department of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital, Dhaka, Bangladesh from January to September 2017. Adult ( $\geq 18$  years), type 2 diabetic patients, who were detected as diabetic for the first time within the previous three months and who tested, at least, two urine samples for urine albumin to creatinine ratio (UACR) (at least 6 weeks apart) were

consecutively enrolled for the study. Pregnant ladies, patients with diagnosed kidney disease, patients having features of glomerulonephritis and systemic diseases including systemic lupus erythematosus and vasculitis, history of recent fever, urinary tract infection and menstruation were excluded. Patients having UACR  $\geq 30$  mg/g in at least 2 (out of 3, if tested) samples were cases and those with UACR  $< 30$  mg/g were controls. Age, presence of hypertension, dyslipidaemia, smoking, family history of diabetes and diabetic nephropathy, body mass index (BMI) and HbA1c were evaluated as possible risk factors for diabetic nephropathy. Data were analyzed by statistical package for social sciences (SPSS) version 20. After univariate analysis of the pre-determined risk factors, all were combined in a multivariate logistic regression model. Odds ratio (OR), 95% confidence interval (95% CI) and p values were recorded. The study protocol was approved by the Institutional Review Board (IRB) of BIRDEM General Hospital. Informed written consent was obtained from each of the study subjects before enrolment for the study.

#### Results:

Total patients were 224 and among them 150 (67%) were females. Fifty one (22.8%) patients had diabetic nephropathy (cases) and rest 173 patients without diabetic nephropathy were controls. Base-line characteristics of the study participants are shown in Table I.

One hundred and eighty two (81.3%) patients were asymptomatic regarding presentation of diabetes and only six (2.7%) patients presented with complication [abnormal glycaemic status was first identified during acute myocardial infarction and oral glucose tolerance test (OGTT) confirmed diabetes at a later stage] (Table II). Blood glucose values (fasting, 2-hour post glucose) and HbA1c levels are presented in Table II. Besides nephropathy, other common diabetic complications among the study subjects were diabetic retinopathy (30, 13.4%) and coronary artery disease (CAD) (20, 8.9%) (Table II).

Most (173, 77.2%) patients had normal UACR. Distribution of study subjects according to UACR is presented in Table III. Most (118, 52.7%) patients had an estimated glomerular filtration rate (eGFR) [calculated by 2009 chronic kidney disease-epidemiology (CKD-

EPI) creatinine-based equation] of  $e^{-60}$  ml/min/1.73 m<sup>2</sup> and only 6 (2.7%) patients had eGFR  $<60$  ml/min/1.73 m<sup>2</sup> (Table IV).

On univariate analysis, hypertension, smoking, family history of diabetes and diabetic nephropathy,

dyslipidaemia, higher BMI and high HbA1c were significant (Table V). On multivariate logistic regression, it was found that, hypertension, smoking, family history of diabetes and diabetic nephropathy, dyslipidaemia, BMI and high HbA1c appeared as significant (Table VI).

**Table-I**

<i>Base-line characteristics of study participants (N = 224)</i>			
Characteristics	Cases = 51	Control = 173	p value
Age (mean±SD) (years)	46.5±9.3	43.9±10.2	0.355
Male/Female (number)	20/31	54/119	0.068
Family history of diabetes mellitus	38 (74.5%)	96 (55.5%)	0.001
Family history of diabetic nephropathy	29 (29/38, 76.3%)	40 (40/96, 41.7%)	0.014
Past history of gestational diabetes	7 (7/31, 22.6%)	18 (18/119, 15.1%)	0.053
Hypertension	24 (47.1%)	33 (19.1%)	0.003
Dyslipidaemia	19 (37.3%)	34 (19.7%)	0.001
Smoker	13 (25.5%)	16 (9.2%)	0.001
Body mass index <sup>20</sup>			
Underweight (<18.5 kg/m <sup>2</sup> ) (1)	-	1 (0.6%)	0.580
Normal weight (18.5–22.9 kg/m <sup>2</sup> ) (29)	2 (3.9%)	27 (15.6%)	0.029
Overweight (23–24.9 kg/m <sup>2</sup> ) (79)	7 (13.7%)	72 (41.6%)	0.0003
Mean±SD	26.62±2.47	24.70±1.87	0.0001

**Table-II**

<i>Clinical presentation, glycaemic profile and chronic complications of the study participants (N = 224)</i>			
Features/glycaemic status	Cases = 51	Controls = 173	p value
Presentation			
Asymptomatic	42 (82.4%)	140 (80.9%)	0.809
Classical	4 (7.8%)	32 (18.5%)	0.068
With complication	5 (9.8%)	1 (0.6%)	0.004
Atypical	-	-	-
Glycaemic status (Mean±SD)			
Fasting blood glucose (mmol/L)	9.93±2.67	9.96±3.05	0.094
Blood glucose value 2-h after 75 gm glucose intake (mmol/L)	16.00±2.92	16.45±4.01	0.457
HbA1c (%)	7.52±4.46	7.40±8.2	0.079
Chronic complications of diabetes mellitus			
Retinopathy	18 (35.3%)	12 (6.9%)	0.034
Neuropathy	8 (15.7%)	3 (1.7%)	0.003
Nephropathy	51 (100%)	-	-
Coronary artery disease	8 (15.7%)	12 (6.9%)	0.55
Stroke/transient ischaemic attack	-	-	-
Peripheral vascular disease	-	-	-

**Table-III**

<i>Status of albuminuria of the study participants (N = 224)</i>		
Status of albuminuria	Frequency	Percentage
Normoalbuminuria (UACR <30 mg/g)	173	77.2
Microalbuminuria (UACR 30-299 mg/g)	47	21.0
Overt-proteinuria (UACR $\geq$ 300 mg/g)	4	1.8

**Table-IV**

<i>Distribution of patients according to estimated glomerular filtration rate (eGFR) (N = 224)</i>			
eGFR range, ml/min/1.73 m <sup>2</sup>	Cases = 51	Controls = 173	p value
$\geq$ 90	21 (41.2%)	81 (46.8%)	0.481
60-89	26 (51.0%)	90 (52.0%)	0.90
45-59	3 (5.9%)	1 (0.6%)	0.012
30-44	1 (2.0%)	1 (0.6%)	0.358
15-29	-	-	-
<15	-	-	-

**Table-V**

<i>Risk factors for diabetic nephropathy (univariate analysis) among newly diagnosed type 2 diabetic subjects</i>					
Risk factor	Cases (n = 51)	Controls (n = 173)	Odds ratio (OR)	95% confidence interval (CI)	p value
<b>Age</b>					
>45 (99)	28	71	1.74	0.93 to 3.28	0.081
$\leq$ 45 (125)	23	102			
<b>Sex</b>					
Male (74)	20	54	1.42	0.74 to 2.71	0.286
Female (150)	31	119			
<b>Hypertension</b>					
Present (57)	24	33	3.77	1.93 to 7.35	0.0001
Absent (167)	27	140			
<b>Dyslipidaemia</b>					
Present (53)	19	34	2.42	1.22 to 4.79	0.01
Absent (171)	32	139			
<b>Smoker</b>					
Yes (29)	13	16	3.35	1.48 to 7.56	0.003
No (195)	38	157			
<b>Family history of diabetes mellitus</b>					
Yes (134)	38	96	2.34	1.16 to 4.70	0.0106
No (90)	13	77			
<b>Family history of diabetic nephropathy (n = 134)</b>					
Yes (69)	29	40	4.51	1.92 to 10.56	0.005
No (65)	9	56			
<b>BMI (kg/m<sup>2</sup>)</b>					
$\geq$ 23.0 (193)	49	144	4.93	1.13 to 21.44	0.033
<23.0 (31)	2	29			
<b>HbA1c (%)</b>					
$\geq$ 7 (160)	44	116	3.08	1.30 to 7.28	0.01
<7 (64)	7	57			

BMI – body mass index, HbA1c – glycated haemoglobin

**Table-VI**

*Multivariate regression analysis for the risk factors for diabetic nephropathy among newly diagnosed type 2 diabetic subjects*

Risk factors	Odds ratio	95% confidence interval	p value
Age	0.51	0.30 to 0.76	0.344
Sex (male)	1.33	0.97 to 1.64	0.067
Hypertension	3.71	1.23 to 4.31	0.003
Smoking	3.27	2.91 to 4.79	0.003
Family history of diabetes	2.31	1.84 to 3.14	0.005
Family history of diabetic nephropathy	3.34	2.40 to 4.97	0.001
Dyslipidaemia	2.31	1.98 to 3.91	0.023
Body mass index	2.11	1.54 to 4.87	0.001
HbA1c	3.21	1.71 to 5.97	0.034

HbA1c – glycated haemoglobin

#### **Discussion:**

The findings from the present research work revealed that nearly 23% of newly detected T2DM patients fulfilled criteria for diabetic nephropathy. During evaluation of risk factors for diabetic nephropathy among them, it was found that, family history of diabetes and diabetic nephropathy, smoking, hypertension, dyslipidaemia, BMI and HbA1c were significant.

Mean age of the present study subjects was nearly 45 years and two-thirds were females. In a study from Uganda, it was found that over 51% of newly detected diabetic patients were males with mean age of 46 years<sup>18</sup> while over two-thirds were males in a study in India.<sup>21</sup> An Egyptian report showed two-thirds of newly detected diabetic patients being females and mean age was over 48 years.<sup>2</sup> Bansal et al reported female predominance (59%) of newly detected diabetic patients in another Indian report with mean age of nearly 50 years.<sup>22</sup> Increased age is an established risk factor for diabetic nephropathy and this observation appeared true for the newly detected diabetic patients also, as revealed in several other studies.<sup>16,17,22</sup>

Family history of DM and diabetic nephropathy were reported as risk factors for diabetic nephropathy, both in established diabetic cases and among newly detected T2DM cases<sup>4,15-18</sup> and findings of the present investigation are in line of this statement. One-sixth of the female patients also had a past history of gestational

diabetes mellitus in the present report. 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.<sup>23</sup>

Present study revealed that over half of the study participants were obese and one-third were over-weight, one-fourth had hypertension and nearly one-fourth had dyslipidaemia. Presence of hypertension, dyslipidaemia and increased BMI were identified as significant risk factors for diabetic nephropathy in the present study. Dyslipidaemia was identified as a significant association for diabetic nephropathy in a study performed in Egypt.<sup>2</sup> Hypertension was reported as a significant risk factor for diabetic nephropathy in several reports among newly detected diabetic patients.<sup>16,17,21</sup> Hypertension can cause CKD, proteinuria, aggravate retinopathy and adversely influence the overall outcome. Antihypertensive medications reduce proteinuria and this effect is prominent for angiotensin receptor inhibitors (ACEIs), angiotensin receptor blockers (ARBs)<sup>19</sup> and non-dihydropyridine calcium channel blockers. Increased BMI was a significant risk factor for diabetic nephropathy in reports of others including those by Rahman et al and Agarwal et al.<sup>16,17</sup>

Almost 13% of newly detected diabetic patients were smokers in this study and this rate was over 25% for those having diabetic nephropathy. Smoking is an established risk factor for diabetic nephropathy.



Aboelnasr et al reported that non-smoking was protective against diabetic nephropathy among newly diagnosed T2DM patients in Egypt.<sup>2</sup>

Over four-fifths of newly detected diabetic patients were diagnosed during some routine investigations for some other reasons in this study. Six of the patients of current study were detected as having an abnormal glycaemia during an acute coronary event. Regarding chronic complications of DM, over 13% had diabetic retinopathy and 5% had neuropathy, both were more common among those having nephropathy. This observation was in agreement with findings by Heydari et al and Deepa et al from Iran and India respectively.<sup>9,10</sup> Diabetic nephropathy and diabetic retinopathy are common outcomes of similar risk factors and diabetic retinopathy is a predictor for diabetic nephropathy.

Long duration of diabetes and poor glycaemic controls are independent risk factors for diabetic complications including diabetic nephropathy.<sup>4</sup> T2DM patients with duration of diabetes for 3 months or less were included in this study. It is not possible to say definitely that for how long these patients were having abnormal glycaemic status. Mean HbA1c of the current newly detected diabetic cohort was just over 7.4%. Mean HbA1c was 8.6% in an Egyptian cohort<sup>2</sup> while it was 13.9% in another cohort from Uganda.<sup>18</sup> We found high HbA1c in our patients as a significant risk factor for diabetic nephropathy, which is in line of other reports.<sup>2,16,17</sup>

Presence of abnormal UACR in two (out of three, if required) samples were used to diagnose diabetic nephropathy and patients having clinical and laboratory features of glomerulonephritis were excluded; it is not certain that none of the patients had other causes of proteinuria, as many were hypertensive. None of our study subjects underwent a kidney biopsy, so any concomitant disease like minimal change disease could not be excluded with confidence. As the present study was a done in a tertiary care hospital, it is understandable that, the findings from this study should not be generalized for all Bangladeshi newly diagnosed T2DM patients.

From the findings of the present study, it can be concluded that, almost 23% newly diagnosed type 2 diabetic patients had diabetic nephropathy; most of the patients had microalbuminuria and only 2% patients

had overt proteinuria. Regarding risk factors for diabetic nephropathy, hypertension, dyslipidaemia, smoking, family history of diabetes and diabetic nephropathy, high BMI and high HbA1c were significant. It is emphasized that, all type 2 diabetic patients should be tested for UACR for evaluation of diabetic nephropathy during their diabetes detection, otherwise they will remain beyond proper evaluation and many diabetic nephropathy cases will be missed. It is recommended that modifiable risk factors like obesity, status of glycaemic control, hypertension, dyslipidaemia and smoking should be identified and intervened.

#### **Acknowledgement:**

We express our acknowledgements to Samira Humaira Habib, Senior Research Officer, Health Economics Unit of Bangladesh Diabetic Society (BADAS) and Professor Md. Mozammel Haque, Professor of Biochemistry, Bangabandhu Sheikh Mujib Medical University (BSMMU) for their suggestions and assistance in analyzing and interpretation of data.

**Conflicts of interest:** Nothing to declare.

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