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Evaluation of Common Risk Factors of Diabetic Nephropathy among Diabetic Adults

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Abstract **Original Research Article**

Background: Diabetic nephropathy (DN) is a specific micro vascular complication of diabetes mellitus (DM), approximately one third of affected diabetic patients eventually develop DN. The level of albuminuria is highly correlated with the intraglomerular pressure which is the key determinant of DN. A number of risk factors were suggested for the development of DN. ***Objective*:** To evaluate the common risk factors of diabetic nephropathy and to determine the association of different risk factors with diabetic nephropathy among adult diabetic patients. ***Methods*:** This cross-sectional study was conducted at the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. A total of one hundred twenty-eight (128) adult diabetic patients were enrolled. We identified nephropathy among them by doing albumin creatinine ratio (ACR) on spot urine and carried out relevant laboratory investigations. Common risk factors of diabetic nephropathy like- hypertension (HTN), overweight/obesity, family history of HTN/DM/DN, duration of DM, glycated hemoglobin (HbA_1C) and dyslipidemia were evaluated accordingly. ***Result*:** Among 128 study population, 52 (40.6%) patients were found to have diabetic nephropathy. Of them, 27.3% had microalbuminuria, 13.3% had macroalbuminuria. Hypertension, overweight/obesity, family history of HTN/DM and dyslipidemia were observed to be significantly higher in nephropathy group than those in the non-nephropathy group ($p<0.05$). Hypertension, dyslipidemia and duration of diabetes mellitus were the independent predictors for diabetic nephropathy. ***Conclusion*:** The prevalence of diabetic nephropathy is high (40.6%) among diabetic adults. Several risk factors are significantly associated with diabetic nephropathy. Hypertension, dyslipidemia and duration of diabetes mellitus are the independent predictors for diabetic nephropathy.

Keywords: Albuminuria, Diabetic Nephropathy (DN), Dyslipidemia, Glycated Hemoglobin (HbA_1C), Hypertension.

1. INTRODUCTION

Diabetes mellitus (DM) is a long-term metabolic disorder marked by high blood glucose (blood sugar). Serious damage to different organs such as heart, blood vessels, eyes, kidneys and nerves can result from diabetes over time [1]. The most prevalent verity type 2 diabetes mellitus (T2DM) usually affects adults and is brought on by insulin resistance to the body or insufficient insulin production in the body [2]. Over the last three decades T2DM has become much more common in all nations, regardless of economic status [3]. Diabetic nephropathy (DN) is a clinical syndrome characterized by persistent proteinuria, progressive decline in the glomerular filtration rate (GFR) and elevated arterial blood pressure [4]. About one third of affected diabetic patients, eventually develop diabetic nephropathy (DN) and have progressive deterioration of renal function [4, 5]. It was reported that, diabetic nephropathy (DN) occurs in 20-40% of patients with diabetes and is the single leading cause of end stage renal

disease (ESRD) [5, 6]. Eventually about 20% patients of type 2 diabetes mellitus (T2DM) reach ESRD during the life time [6]. Studies conducted in migrant Asian Indians in Europe have reported increased prevalence of diabetic nephropathy compared with white Caucasians [7-9]. The incidence of diabetic kidney disease among the Asians is higher than Dutch-European diabetic patients [9]. It was documented that, the pathological changes in the kidneys, clinical stages and risk factors to develop diabetic nephropathy are similar in both types of diabetes [10-12]. The pathogenesis responsible for diabetic nephropathy largely depends on hyperglycemia resulting in non-enzymatic glycation and the accumulation of advanced glycation products [10-12]. There are five distinct stages of diabetic nephropathy [6]. Stages one and two are clinically silent. In the third stage, which is referred to as incipient nephropathy and is characterized by microalbuminuria, blood pressure tends to increase. At stage IV; there is an overt nephropathy; macroalbuminuria is present, blood pressure almost invariably increases and renal function particularly glomerular filtration rate (GFR) progressively declines. In stage V, renal failure is present. The development of diabetic nephropathy (DN) is known to be significantly influenced by a number of risk factors, the most important of which is hypertension (HTN) [6]. Besides, several studies suggested that poor glycemic control, dyslipidemia, and duration of diabetes had detrimental effect on the progression of diabetic nephropathy [6, 11, 13]. The prevalence of microalbuminuria, overt proteinuria or diabetic nephropathy and its association with risk factors have not yet been studied adequately among adult Bangladeshi population. The current study was aimed to evaluate the common risk factors of diabetic nephropathy and to determine the association of different risk factors with diabetic nephropathy among Bangladeshi adults.

2. METHODOLOGY

This cross-sectional study was conducted at the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. A total of one hundred twenty-eight (128) adult diabetic patients were enrolled for this study. Adult (age >18 years) type- 2 diabetic patients without recent history of fever, urinary tract infection, pregnancy and evidence of other renal diseases were included. Patients with other co-morbid diseases (like- hepatic, other systemic diseases or any type of malignancy) were excluded from the study. Informed written consent was taken from each participant prior to the enrollment. All study participants were evaluated by history, clinical examination and investigations. Relevant clinical and laboratory data were obtained from the medical records of the patients. Particulars of the patient including age, sex, and relevant medical history including- hypertension (HTN), duration of diabetes mellitus (DM), family history of HTN/DM/DN, other long-term complications of DM and ongoing drug history were recorded accordingly. Anthropometric measurements were taken, including weight and height to estimate body mass index (BMI) [Kg/m^2]. 'Overweight' was labeled as having a BMI of 25.0-29.9 Kg/m^2, and obesity as having a BMI of ≥30 Kg/m^2 according to the World Health Organization (WHO) classification of BMI [14]. Blood pressure was measured using standardized Sphygmomanometer. Fasting blood glucose, 2-hour post-prandial blood glucose, serum creatinine, serum total cholesterol, serum triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were assayed by enzymatic methods with an automatic analyzer (Hitachi 7600-020, Hitachi Co., Tokyo, Japan). Patient with any of these underling values was considered to have dyslipidemia: LDL-C >100 mg/d1, triglyceride >150 mg/d1 HDL-C <40 mg/d1 [16]. Glycated hemoglobin (HbA_1C) was estimated by high-performance liquid chromatography (HPLC) method (Bio-Rad); HbA_1C was considered within normal limit if <7% [16]. Fresh random morning spot urine was examined by the dipstick test for proteins, leucocytes, nitrites, erythrocytes etc. Urine albumin creatinine ratio (ACR) was done to level the proteinuria. Spot urine albumin creatinine ratio (ACR) less than 30 mg/g was referred to normoalbuminuria [5]. Microalbuminuria was diagnosed when the urinary albumin to creatinine ratio was 30 - 299 mg/g in at least two of three urine collections. Whereas to designate a patient as having macroalbuminuria the same ratio was ≥300 mg/g. Diabetic nephropathy (DN) was defined as appearance of albuminuria on at least two separate occasions, two weeks apart [5]. Presence of common risk factors (such as hypertension, dyslipidemia, overweight/obesity, duration of diabetes and poor control of diabetes) of diabetic nephropathy were evaluated accordingly.

Statistical analysis

Data were processed and analyzed with the help of computer-based software Statistical Package for Social Sciences (SPSS), version 26. The test statistics used to analyze the data were descriptive statistics. The data presented on categorical scale were expressed as frequency and corresponding percentages and were compared between groups using Chi-square (x^2) test, while the data presented on continuous scale were expressed as mean with standard deviation (SD) and compared among groups using ANOVA test. The risk factors that were found to be associated with diabetic nephropathy in univariate analysis were further subjected to analyze in the multivariate binary logistic regression model to find out the independent predictors of diabetic nephropathy. A p value <0.05 was considered as statistically significant.

3. RESULTS AND OBSERVATIONS

This current study was intended to assess common risk factors of diabetic nephropathy (DN) among diabetic patients. A total of 128 adult diabetic (T2DM) patients were enrolled. Of them, 52(40.6%)

patients were found to have diabetic nephropathy and 76(59.4%) patients didn't develop diabetic nephropathy (non-nephropathy group) (Figure- 1). Among the study population, 27(51.9%) were male and 25(49.1%) were female in diabetic nephropathy group; on the other hand, 40(52.6%) were male and 36(47.4%) were female in non-nephropathy group (Figure-2).

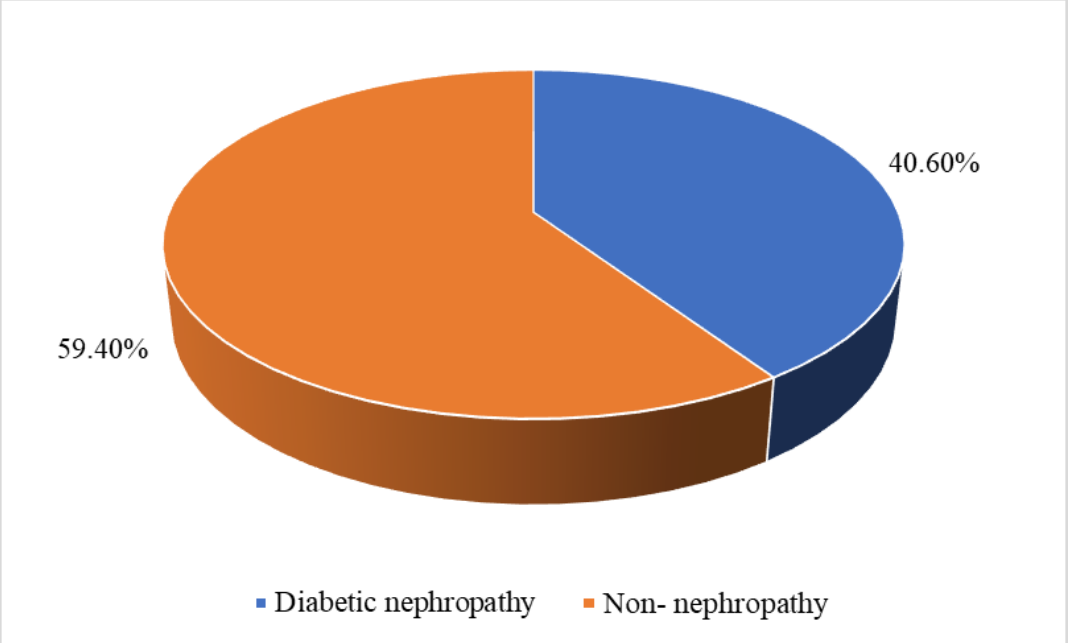

Figure-1: Prevalence of diabetic nephropathy among the study population (N= 128)

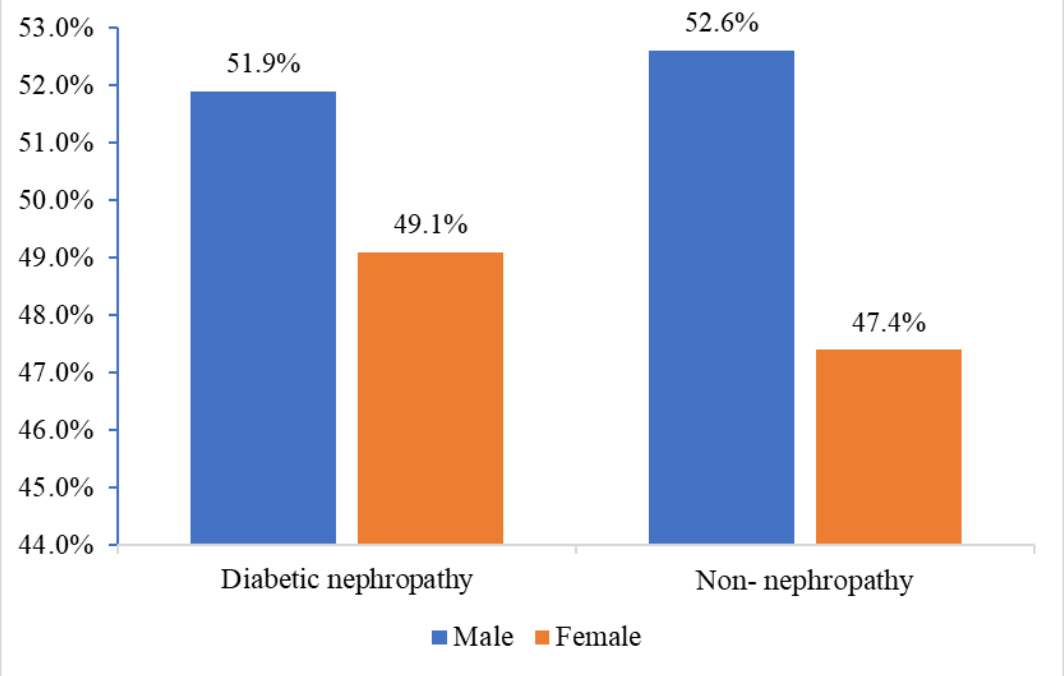

Figure-2: Gender distribution among the groups of study population (N= 128)

It was observed that, 76(59.4%) study population had normoalbuminuria, while 35(27.3%) had microalbuminuria and 17(13.3%) had macroalbuminuria (Figure-3). Staging of chronic kidney disease (CKD) using Cockcroft-Gault formula showed that 24(18.8%) study patients were in CKD stage- I, 15(11.7%) were in stage- II, 10(7.8%) were in stage- III, 3(2.3%) were in stage- IV and 76(59.4%) study patients were free from CKD (Figure-4).

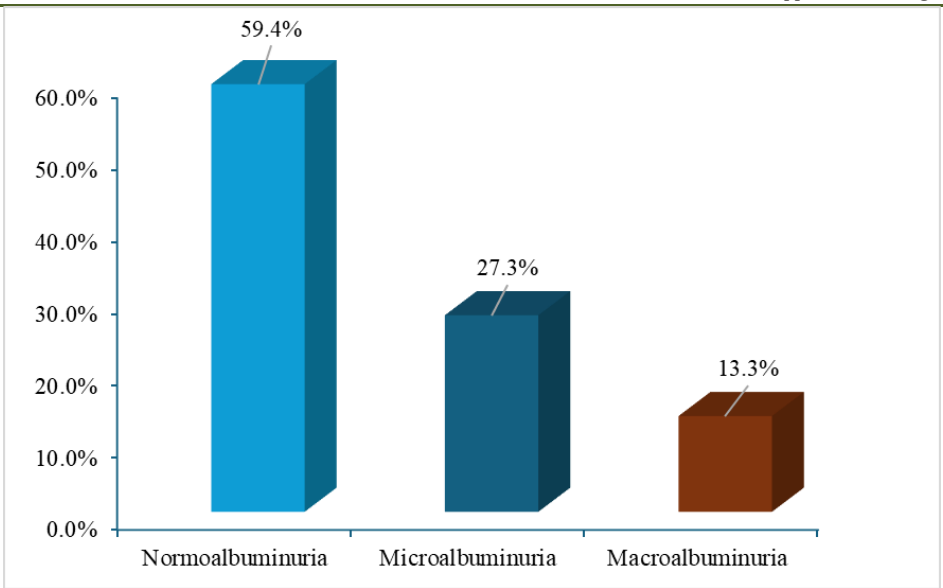

Figure-3: Distribution of study population according to albuminuria (N= 128)

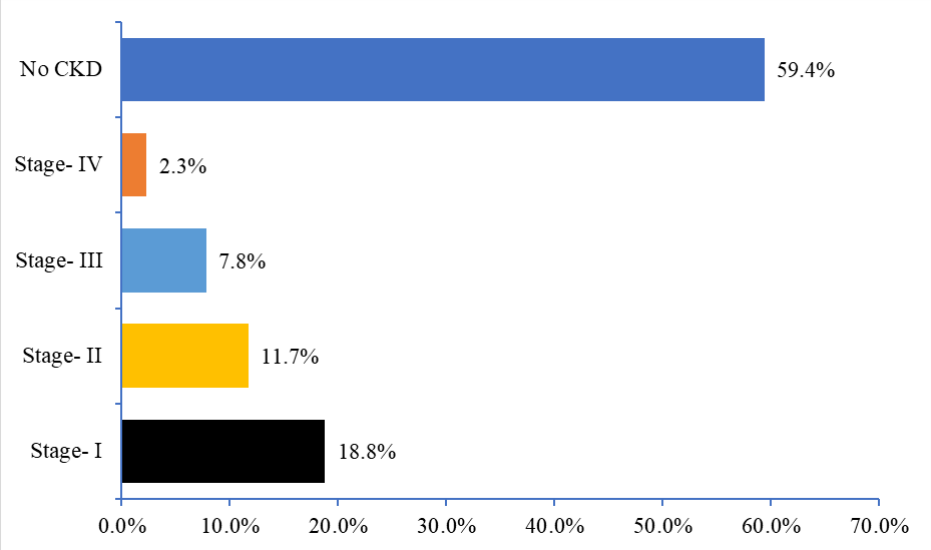

Figure-4: Distribution of the study population on CKD staging (N= 128)

Among the total study population; 41.4% was hypertensive, 36.7% had family history of diabetes mellitus, 18.8% had family history of hypertension, 12.5% had overweight/obesity and 7% had family history of diabetic nephropathy (Table-1).

Table-1: Distribution of study patients on presence of clinical risk factors (N = 128)

Presence of risk factors	Frequency (n)	Percentage (%)
Hypertension	53	41.4
Family history of DM	47	36.7
Family history of HTN	24	18.8
Overweight/obesity	16	12.5
Family history of DN	09	7.0

In this study; hypertension, overweight/obesity, family history of diabetes mellitus and family history of hypertension were observed to be significantly higher in the nephropathy group than those in the non-nephropathy group ($p < 0.001$, $p = 0.014$, $p = 0.027$ and $p = 0.001$ respectively). However, family history of diabetic nephropathy was not found to be associated with developing nephropathy ($p = 0.536$) (Table- 2).

Table-2: Factors associated with the diabetic nephropathy (N =128)

Factors	Nephropathy (n= 52)	Non-nephropathy (n= 76)	p-value*
Hypertension	36(69.2)	17(22.4)	<0.001
Overweight/obesity	11(21.1)	5(6.6)	0.014
Family history of DM	27(51.9)	20(26.3)	0.027
Family history of hypertension	17(32.7)	7(9.2)	0.001
Family history of DN	4(7.7)	5(6.6)	0.536

Figures in the parentheses indicate corresponding percentage, *Chi-square (x^2) test was performed

Three lipids namely triglyceride (TG), LDL cholesterol and HDL cholesterol were studied between the subjects with and without nephropathy. Nearly 60% of the nephropathy group had TG >150 mg/dl as opposed to 25% of the non-nephropathy group (p<0.001). The level of LDL cholesterol more than 100 mg/dl was also observed to be significantly higher (p<0.001) among the nephropathy group (80.8%) than that in the non-nephropathy group (35.5%). The proportion of subjects with HDL cholesterol less than 40 mg/dl was also significantly higher in the former group (53.8%) than that in the latter group (28.9%) (p= 0.005) (Table-3).

Table-3: Association between dyslipidemia and diabetic nephropathy (N = 128)

Dyslipidemia	Nephropathy (n= 52)	Non-nephropathy (n= 76)	p-value
TG >150 mg/dl	31(59.6)	19(25.0)	<0.001
LDL-C>100 mg/dl	42(80.8)	27(35.5)	<0.001
HDL-C<40 mg/d1	28(53.8)	22(28.9)	0.005

Figures in the parentheses indicate corresponding percentage,
Chi-square (x^2) test was performed to analyze the data

Comparison of different risk factors between the levels of proteinuria (nephropathy and non-nephropathy groups) showed that elderly subjects (age >60 years) developed nephropathy (36.5%) significantly more than the subjects age 60 years or below (18.4%) (p= 0.007). Hypertension was significantly higher among patients with microalbuminuria than that of patients without microalbuminuria and was even higher in patients with overt albuminuria (p<0.001). Proteinuria was significantly higher among overweight/obese diabetic patients (p<0.001). Patients with uncontrolled diabetes as indicated by HbA_IC (>7%) was significantly higher in microalbuminuria group than patients without microalbuminuria and that was even higher in patients with overt proteinuria (p<0.001). The mean duration of diabetes was significantly lowest in patients with ACR <30 mg/g (2.5±0.7 years) and highest in patients with ACR ≥300mg/g (8.5±1.8 years) (p<0.001). The prevalence of dyslipidemia (high triglyceride, high LDL cholesterol and low HDL cholesterol level) was also found to be increased with the increasing urine ACR level (p<0.001) (Table-4).

Table-4: Association of risk factors with different levels of proteinuria (N = 128)

Risk factors	Urine ACR (mg/g)			p-value
	<30 (n= 76)	30-299 (n= 35)	≥300 (n= 17)	
Age >60 years	14(18.4)	16(45.7)	3(17.6)	0.007*
Hypertension	17(22.4)	23(65.7)	13(76.5)	<0.001*
Overweight/obesity	5(6.6)	6(17.1)	5(29.4)	<0.001*
HbA_IC>7%	31(40.8)	22(62.9)	17(100.0)	<0.001*
Duration of DM (years)	2.5±0.7	7.6±2.2	8.5±1.8	<0.001**
TG >150 mg/dl	19(25.0)	18(51.4)	13(76.5)	<0.001*
LDL-C>100 mg/dl	27(35.5)	27(77.1)	15(88.2)	<0.001*
HDL-C<40 mg/dl*	22(28.9)	16(45.7)	12(70.6)	<0.001

Figures in the parentheses indicate corresponding percentage, *Chi-square (x^2) test was performed,
**Data were analyzed by ANOVA test and were presented as mean±SD

The variables revealed to be significantly associated with nephropathy by univariate analysis were all entered into the multivariate logistic regression analysis model. Of the 5 variables (Age, HbA_IC, dyslipidemia, hypertension, duration of diabetes); dyslipidemia, hypertension and duration of diabetes were

found to be the independent predictors for developing diabetic nephropathy with odds ratios (OR) were 3.9, 3.4 and 1.3 respectively. The ORs indicate that patients with dyslipidemia were 3.9 times higher risk of developing diabetic nephropathy than patients without dyslipidemia (p= 0.009). Patients with hypertension were also at 3.4 times higher risk of developing diabetic nephropathy (p=0.014) than those without hypertension. The likelihood of developing nephropathy in patients with longer duration of diabetes was 1.3 times higher than those in patients with shorter durations of diabetes (p= 0.003) (Table- 5).

Table-5: Multivariate logistic regression analysis of risk factors in diabetic nephropathy (N = 128)

Risk factors	Univariate analysis (p-value)	Multivariate analysis	
		Odds Ratio (95% CI of OR)	p-value
Age (>60 years)	0.021	2.1(0.75-6.03)	0.157
HBA_IC (>7%)	<0.001	2.6(0.95-7.1)	0.064
Dyslipidemia	<0.001	3.9(1.4-11.2)	0.009
Hypertension	<0.001	3.4(1.2 -9.2)	0.014
Duration of diabetes (>5 years)	0.027	1.3(1.1-1.6)	0.003

4. DISCUSSION

Globally, diabetic nephropathy is the leading cause of end stage kidney failure [17]. Every year, more than 50% of diabetic patients enroll in dialysis or transplant programs [18]. Over the previous 30 years, there has been a notable increase in the prevalence of diabetic kidney disease [7]. There are several risk factors that are known to have a significant impact on the development of diabetic nephropathy (DN). The main etiological factors for the onset of diabetic nephropathy are chronic hyperglycemia and hypertension [17]. This current study enrolled 128 adult type 2 diabetic patients to evaluate the risk factors of diabetic nephropathy. In this study prevalence of DN was 40.6%. Of this, the prevalence of overt diabetic nephropathy was 13.3% and that of incipient nephropathy was 27.3%. One previous study showed that prevalence of overt nephropathy was 2.2% and that of microalbuminuria was 26.9% in urban Indians [13]. Another related study reported that, 23% diabetic patients had overt proteinuria [19]. In a previous study, 39% of diabetic people was found to have microalbuminuria and 19% had overt proteinuria [8]. Prevalence of DN was slightly lower in our study. But diabetic nephropathy was found higher in a couple of previous study [20-21]. The variations observed in the prevalence of diabetic nephropathy among different studies could be due to differences in study design and sample size.

There are several known risk factors of diabetic nephropathy among diabetic patients. In this study, we searched for the presence of common risk factors of DN among adult diabetic patients and evaluated the association of these risk factors with diabetic nephropathy. The risk factors like- old age, poor glycemic control, long duration of diabetes, hypertension, and dyslipidemia were found significantly higher in both overt and incipient nephropathy. These findings were supported by a couple of related previous studies [6, 11, 13, 20].

Hypertension accelerates kidney dysfunction in patients with diabetic mellitus. Normalization of blood pressure retards the progression of diabetic nephropathy. In our study, 41.4% of diabetic patients had hypertension. Hypertension was significantly higher in nephropathy group (p<0.001). Among nephropathy group hypertension was significantly higher in patients with macroalbuminuria (p<0.001). It was documented that, prevalence of hypertension was significantly higher among subjects with micoralbuminuria and overt nephropathy compared with the normoalbuminuria group (p<0.001) [13]. In a related study, it has been found that prevalence of hypertension in diabetic patients was 58% [22]. In accordance, another study showed that 52% hypertensive diabetic patients had proteinuria [19]. In our study, aged diabetic patients (>60 years.) had tendency to develop nephropathy. In this context, it was shown that old age was an independent risk factor for diabetic nephropathy [23, 24]. Among the common risk factors; family history of diabetes mellitus, family history of hypertension, overweight/obesity and family history of diabetic nephropathy were 36.7%, 18.8%, 12.5%, and 7% respectively in this present study. Hypertension, overweight/obesity, family history of diabetes mellitus and family history of hypertension were found significantly higher among nephropathy group (p<0.001, p= 0.014, p= 0.027, p=0.001 respectively). These results were consistent with a similar previous study [25].

Duration of diabetes mellitus plays crucial role for the development of diabetic nephropathy. In this current study, the mean duration was highest in patients with macroalbuminuria (8.5±1.8 years) and lowest (2.5±0.7 years) in patient with incipient nephropathy (p<0.001). Study on urban Indian population demonstrated that, there was an increase in the prevalence of microabuminuria and macroalbuminuria with the increasing in duration of diabetes [20].

Metabolic risk factors including poor glycemic control and dyslipidemia were associated with diabetic

nephropathy. Several studies on diabetic patients have revealed a beneficial effect of good glycemic control on rate of progression of microalbuminuria to overt nephropathy [25-28]. These factors like- glycated hemoglobin (HbA_1C) and dyslipidemia have great influence on diabetic nephropathy. In this link; one previous study revealed that higher initial values of HbA_1C, LDL cholesterol, triglyceride were significantly associated with progression of diabetic nephropathy [25]. Several studies found that poor long term glycemic control, indicated by the concentration of glycated hemoglobin (HbA_1C), was an important predictor of the development of albuminuria both in non-insulin dependent and insulin dependent diabetes mellitus [26-29]. Our study also found that about 54.7% of study population had poor glycemic control as indicated by HbA_1C. Patients with raised HbA_1C level (>7%) was also higher in nephropathy group (75%) comparison to non-nephropathy group (40.8%). Uncontrolled diabetes as indicated by the concentration of HbA_1C tends to be associated with the development of nephropathy significantly more than their controlled counterpart (non-nephropathy group) ($p<0.001$). But HbA_1C was not an independent risk factor of diabetic nephropathy in our study. It was reported that, the prevalence of hyperglycemia in both microalbuminuria and overt proteinuria was significantly increased with the increasing HbA_1C level ($p<0.001$) [13].

Dyslipidemia may be responsible for glomerular injury and lipoproteins are also associated with microvascular changes in diabetic patient [30]. The prevalence of triglyceride more than 150 mg/dl and LDL cholesterol more than 100 mg/dl were found to be increased with the increase of urinary albuminuria ($p<0.001$). Previous study confirmed that base line elevated total cholesterol, LDL cholesterol and triglyceride levels were associated with and increased risk of the development of ESRD in patients with type 2 diabetes mellitus [31]. Multivariate analysis of risk factors in our study showed that dyslipidemia was the independent risk factor for albuminuria. Ravid *et al*., also documented that dyslipidemia was significantly related with the increase in urinary albumin concentration in diabetic nephropathy [25].

To determine the predictive risk factor for diabetic nephropathy we carried out multivariate binary logistic regression analysis. The study revealed that hypertension, duration of diabetes and dyslipidemia were the predictors for diabetic nephropathy. These findings were consistent with similar previous studies [25, 32, 33]. In a related study on 574 diabetic patients, logistic regression analysis highlighted the role of glucose control along with lipid profile and mean blood pressure as joint major risk factors for subsequent renal outcome [25]. Another study showed that, systolic blood pressure to be an independent risk factor for the relative rate of increase of the urinary albumin concentration [32]. A higher mean arterial blood pressure was also reported a risk factor for development of diabetic nephropathy [33]. It was reported that dyslipidemia, HbA_1C concentration and old age were the independent risk factors for the development of nephropathy [24].

5. CONCLUSION

The current study concluded that prevalence of diabetic nephropathy is high in adult diabetic patients. Hypertension, dyslipidemia and duration of diabetes mellitus are the independent predictors for diabetic nephropathy among adult diabetic patients. Old age, poor glycemic control, family history of diabetic mellitus, family history of hypertension and overweight/obesity are also associated with diabetic nephropathy.

Limitations of the study: It was a single center study with a relatively small sample size.

Recommendation

A large population based multicenter study on diabetic nephropathy should be done to confirm the findings of this current study.

Conflicts of Interest: The authors declare no conflicts of interest regarding this publication.

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