Original Article

Prevalence of Nephropathy with Evaluation of HbA1c Level and other Associated Risk Factors in Type 2 Diabetic Patients in a Tertiary Level Hospital

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Abstract

Background: *Diabetes is the leading cause of chronic kidney disease which ultimately results end-stage renal disease (ESRD).* ***Objectives:*** *The purpose of the study was to explore the factors influencing or related to the development of the diabetic nephropathy with specific concern to the HbA1c (glycosylated hemoglobin) levels.* ***Methods:*** *Four hundred type 2 diabetic patients (male 166 and female 234) were studied and were evaluated for the presence of nephropathy through the review of their registered diabetic guide book. Glycaemic status was assessed by HbA1c (HbA1c was categorized into 3 groups) and plasma glucose levels. We used Student's t-test, χ^2-test and logistic regression analysis to determine and quantify the association of diabetic nephropathy with various risk factors specially HbA1c.* ***Results:*** *The prevalence of nephropathy was 24.0%; male 27.1%, female 21.8%. Increasing HbA1c categories above 7.0% were significantly associated with increased prevalence of nephropathy (15.8 vs 22.8 vs 30.7%; χ^2 = 8.590, p = .013). Logistic regression models of univariate analysis showed that the risk of nephropathy was strongly increased at the HbA1c categories ≥8% (OR = 2.35; 95% CI: 1.30-4.25). Advanced age (OR = 3.8; 95% CI: 2.21-6.53), longer duration of diabetes (OR = 4.05; 95% CI: 2.31-7.10), lacking of physical exercise (OR = 1.93; 95% CI: 1.20-3.10), presence of hypertension (OR = 4.62; 95% CI: 2.42-8.83), fasting blood glucose (OR = 1.139; 95% CI: 1.054-1.231), blood glucose 2 hours after breakfast (OR = 1.088; 95% CI: 1.028-1.152), systolic blood pressure (OR = 1.049; 95% CI: 1.030-1.069) and diastolic blood pressure (OR = 1.061; 95% CI: 1.026-1.097) had significant association with nephropathy.* ***Conclusion:*** *HbA1c categories >7.0% is an important risk factor for the development of nephropathy.*

Key words: *Nephropathy, HbA1c, Risk factors, Type 2 diabetes.*

Date of received: *16.06.2016*
Date of acceptance: *05.05.2017*

Introduction

The proportion of patients with end-stage renal disease (ESRD) caused by diabetes has progressively increased during the last few decades and diabetic nephropathy (DN) is the leading cause of end stage renal disease (ESRD) in the world. Diabetic nephropathy is defined by persistent albuminuria, declining glomerular filtration rate (GFR) and progressive rise in blood pressure. Approximately 40-50% of patients with type 1 diabetes and 20-30% of patients with type 2 diabetes develop diabetic nephropathy[1]. Based on studies in type 1 diabetes, it had been generally considered that once overt diabetic nephropathy, manifesting as persistent proteinuria, is present, it was only possible to slow, but not halt, the progression toward ESRD[2-4]. This led investigators during the early 1980s to search for early predictors of diabetic nephropathy. Most investigators now agree that diabetic nephropathy result from the

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interaction of multiple metabolic, genetic and other factors of which chronic hyperglycemia is one of the most significant factor in both the initiation and progression of the disease[5]. Different randomized controlled trials and observational studies have strongly suggest that hyperglycaemia or closely associated factors of poor glycaemic control, like HbA1c is a good predictor of diabetic nephropathy[5-9], and is highly correlated with fasting blood glucose (FBG) and does not require measurement in the fasting state[10]. One study showed that increasing HbA1c categories had a higher prevalence of chronic kidney disease (CKD) and micro or macro-albuminuria. In the multivariable models, HbA1c categories above 7.0% were significantly associated with increased prevalence of diabetic nephropathy compared with the lowest category[11]. Another study demonstrated that HbA1c >6.5% predicts a future risk of kidney disease. Above the threshold point with the increasing of HbA1c levels the risk of kidney diseases also increases sequentially[12]. It indicates that HbA1c may be used as a useful marker for nephropathy along with other risk factors. The ADVANCE trial documented that (in subjects with type 2 diabetes mellitus) strict glycaemic control (mean HbA1c: 6.5%) in comparison with standard control (mean HbA1c: 7.3%) is associated with a significant reduction in renal events, including onset of or worsening of nephropathy [hazard ratio (HR) 0.79; P = 0.006], new-onset microalbuminuria (HR 0.91; P = 0.02), and, in particular, development of macroalbuminuria (HR 0.70; P <0.001)[13].

There are several other predictors[14-18] of diabetic nephropathy including advanced age, longer duration of diabetes, body weight, smoking, diabetic ketoacidosis, mild to moderate nonproliferative diabetic retinopathy, proliferative diabetic retinopathy (the most prevalent predictor), proteinuria, hypertension, dyslipidaemia, physical inactivity etc. Both sexes are vulnerable to diabetic nephropathy, although there is an unexplained male preponderance of diabetic nephropathy. Ethnicity and family history also affect the risk of diabetic nephropathy. The burden of nephropathy will increase in future as the incidence of diabetes increases and the age of onset declines, although the effects may be lessened by the use of emerging therapies[19]. Therefore, we attempted to do a clinical study on relation of HbA1c and other risk factors with nephropathy. Our aim was to gain new insights into how different risk factors specially HbA1c affect and reflect the risk of nephropathy among patients with type 2 diabetes.

Materials and Methods

This is a cross-sectional study in type 2 diabetic patients under follow-up in the outpatient department (OPD) of BIRDEM hospital from January 2014 to December 2014. The study enrolled 400 type 2 diabetic patients of both gender and age group 30-60 years as study participants. The average duration of type 2 diabetes for the population was approximately 6.41 years ranging from 2 to 10 years. Patients with other chronic illnesses like chronic hepatic diseases, chronic arthritis etc. those may interfere with the blood glucose levels, pregnant diabetic cases or gestational diabetes, type 1 diabetics and patients of hemoglobinopathies were excluded from the study. We availed the information of the patients from their 'diabetic guide book'. This registered medical record book contained all records of baseline information and recorded necessary advice to diabetes management for subsequent follow-up visit.

In this study we collected data about sociodemographic information (age, sex, family history of diabetes, geographical location, socioeconomic factor, educational history, occupational history), lifestyle characteristics (physical activity, smoking history etc.), blood pressure and anthropometry (height, weight, calculated body mass index) of the participants. The duration of diabetes were also recorded. The selected patients were evaluated for the presence of nephropathy through the review of physicians' notes in the patients' medical report which were recorded in their diabetic guide book. The glycaemic status of the participants were assessed by HbA1c, FBG and 2 hours ABF. In this study we categorized the study participants into 3 groups by 3 HbA1c categories. These were good control group (HbA1c <7.0%), average control group (HbA1c 7-7.9%) and poor control group (HbA1c ≥8.0%). We compared the participants in these 3 HbA1c categories. HbA1c was measured by BIO-RAD variant which was modified HPLC method. Serum creatinine levels and fasting lipid profile were also measured. The prevalence rate of nephropathy among type 2 diabetes was determined by simple percentages. For comparison of different variables among the groups we used Chi-square test for categorical data and Student's t-test for quantitative data. Univariate logistic regression analysis was performed to identify factors associated with nephropathy. Odds ratio (OR) with 95% confidence interval (CI) were provided. All statistical tests were considered significant at a level of $p < 0.05$. SPSS software, version 21 was used for the statistical analysis.

Results

Among the study subjects 41.5% (166) were male and 58.5% (234) were female. The mean age of the study participants during study time was 50.05 (±7.528) years. The range of duration of diabetes was 2-10 years and mean duration was 6.41 (±3.06) years. The overall prevalence of nephropathy was 24.0%; male (27.1%), female (21.8%). Among the study participants the mean HbA1c was 7.99% (±1.80). The details of relationship of nephropathy with HbA1c is shown in table I, III, IV and figure 1. In case of nephropathy the increasing HbA1c categories above 7.0% showed sequentially higher prevalence compared with the lower category (15.8 vs 22.8 vs 30.7%; χ^2 = 8.590, p = .013). We used the univariate logistic regression analysis to quantify the individual effect of HbA1c and other risk factors with nephropathy as dependent variable. HbA1c category ≥ 8% (OR = 2.35; 95% CI: 1.30-4.25) were found to be a significant risk factor for developing nephropathy (Table IV).

Table-I: Relationship between nephropathy and HbA1c categories

HbA 1c categories (%)	With nephropathy (n= 96)	Without Nephropathy (n= 304)	Total	χ^2	p value
<7	19 (15.8%)	101 (84.2%)	120		
7-7.9	26 (22.8%)	88 (77.2%)	114	8.590	**.013**
8	51 (30.7%)	115 (69.3%)	166		
Total	96 (24.0%)	304 (76.0%)	400		

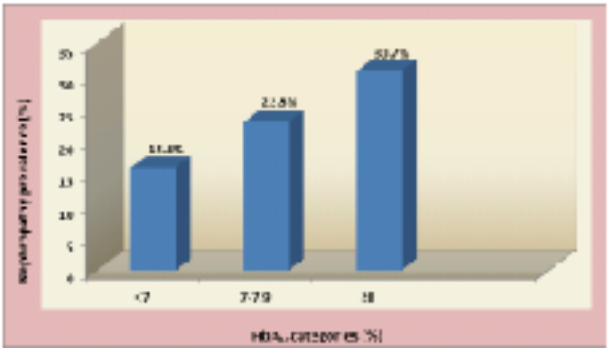

Figure-1: Prevalence of nephropathy at different HbA1c categories

We found significantly higher nephropathy in age group ≥ 50 years than <50 years (33.3 vs 11.6%; χ^2 = 25.323, p =.000). We also found that not urban (suburban and rural) participants demonstrated higher nephropathy than urban counterparts and the difference was significant (38.5 vs 18.6%; χ^2 = 17.347, p = .000). However male female variation and educational status did not show any significant difference. The patients with longer duration of diabetes i.e. 6-10 years (33.2 vs 10.9%; χ^2 = 26.387, p = .000), lacking of regular physical exercise (29.8 vs 17.9%; χ^2 = 7.639, p = .006) and hypertension (31.5 vs 9.0%; χ^2 = 24.505, p = .000) were significantly associated with nephropathy (Table II).

Table-II: Association of different sociodemographic characteristics of the study participants with nephropathy

Variables	Total subjects (n=400)	Nephropathy no of cases (%)	*p* value
Age group (years)			
<50	172	20 (11.6)	**.000**
≥ 50	228	76 (33.3)	
Duration of diabetes (years)			
2-5	165	18 (10.9)	**.000**
6-10	235	78 (33.2)	
Gender			
Male	166	45 (27.1)	.220
Female	234	51 (21.8)	
Residence			
Urban	291	54 (18.6)	**.000**
Not urban	109	42 (38.5)	
Educational status			
Schooling	310	72 (23.2)	.501
No schooling	90	24 (26.7)	
Exercise done by patients			
Yes	195	35 (17.9)	**.006**
No	205	61 (29.8)	
Presence of hypertension			
Yes	267	84 (31.5)	**.000**
No	133	12 (9.0)	

In table III we found that patients with nephropathy showed a significantly higher mean age than the patients without nephropathy (54.05 ± 5.252 vs 48.79 ± 7.701, p = .000). Duration of diabetes (7.95 ± 2.447 vs 5.92 ± 3.087, p = .000) also showed significant difference between the patients with and without nephropathy. HbA1c (8.629 ± 2.083 vs 7.795 ± 1.66, p = .000), FBG (10.057 ± 2.969 vs 8.948 ± 2.725, p = .001), blood glucose 2 hours ABF (14.144 ±3.798 vs 12.743 ± 4.05,

p = .003), SBP (133.65 ± 13.717 vs 125.54 ± 12.137, p = .000) and DBP (83.28 ± 7.808 vs 80.44 ± 6.465, p = .000) were significantly higher in patients with nephropathy. BMI and lipid profile did not show any significant difference.

Table-III: Clinical variables related to nephropathy

Variables	Total participants (n=400)		*p* value
	With Nephropathy (n= 96) Mean ± SD	Without Nephropathy (n= 304) Mean ± SD	
Age (years)	54.05 ± 5.252	48.79 ± 7.701	**.000**
Duration of diabetes (years)	7.95 ± 2.447	5.92 ± 3.087	**.000**
SBP (mm of Hg)	133.65 ± 13.717	125.54 ± 12.137	**.00 0**
DBP (mm of Hg)	83.28 ± 7.808	80.44 ± 6.465	**.000**
HbA 1c(%)	8.629 ± 2.083	7.795 ± 1.663	**.000**
FBG (mmol/L)	10.057 ± 2.969	8.948 ± 2.725	**.00 1**
2 hours ABF (mmol/L)	14.144 ± 3.798	12.743 ± 4.051	**.00 3**

* FBG - Fasting blood glucose, 2 hours ABF - blood glucose 2 hours after breakfast, SBP- Systolic blood pressure, DBP- Diastolic blood pressure.

On logistic regression analysis we observed that advanced age (OR = 3.8; 95% CI: 2.21-6.53), longer duration of diabetes (OR = 4.05; 95% CI: 2.31-7.10), lacking of physical exercise (OR = 1.93; 95% CI: 1.20-3.10), presence of hypertension (OR = 4.62; 95% CI: 2.42-8.83), FBG (OR = 1.139; 95% CI: 1.054-1.231), blood glucose 2 hours ABF (OR = 1.088; 95% CI: 1.028-1.152), SBP (OR = 1.049; 95% CI: 1.030-1.069) and DBP (OR = 1.061; 95% CI: 1.026-1.097) were significant risk factors of nephropathy. When we compared male and female with nephropathy we did not find any significant difference (Table IV).

Table-IV: Univariate logistic regression analysis showing different variables associated with nephropathy

Variables	Odds Ratio (95% CI)	*P*-value
HbA 1c(%)		
<7	1.0	
7-7.9	1.57 (8.14 -3.03)	.178
8	2.35 (1.30 -4.25)	**.00 4**
Age (years)		
<50	1.0	
50	3.80 (2.21 -6.53)	**.000**
Gender		
Female	1.0	
Male	1.334 (0.84-2.11)	.221
Duration of diabetes (years)		
2 -5	1.0	
>6-10	4.05 (2.31 -7.10)	**.00 0**
Exercise done by patients		
Yes	1.0	
No	1.93 (1.20 -3.10)	**.006**
Presence of hypertension		
No	1.0	
Yes	4.62 (2.42 -8.83)	**.000**
FBG	1.139 (1.054 -1.231)	**.00 1**
2hours ABF	1.088 (1.028 -1.152)	**.00 0**
SBP	1.049 (1.030 -1.069)	**.000**
DBP	1.061 (1.026 -1.097)	**.001**

Discussion

In our study the prevalence of nephropathy was 24.0% with male 27.1% and female 21.8%. In a study conducted in India showed the prevalence of nephropathy was 20%[14]. Another study revealed that prevalence of nephropathy was 32.5% in India[15]. A lower prevalence of proteinuria (19.7%) was found in another study[20]. WHO multicentric study of vascular disease in diabetes, observed a wide geographic variation in prevalence of nephropathy i.e. 2.4% from Hong Kong, 23% from Delhi to 37% from Oklahoma, USA[21]. These geographical and population variation in prevalence of diabetic nephropathy could be due to real ethnic variation in the susceptibility to diabetic nephropathy i.e. genetics, poor glycaemic control, hypertension or other socioeconomic, cultural and environmental factors. Several studies indicated that HbA1c may show a glycaemic threshold with micro- and macro-vascular complications of diabetes, suggesting it may additionally be useful biomarker to identify individuals at risk for different vascular complications[11,12,22]. In this study we observed that increasing HbA1c categories above 7.0% were significantly associated with increased prevalence of nephropathy. Logistic regression models of univariate analysis showed that the risk of nephropathy strongly increased at the HbA1c categories $\geq$ 8%. Our results were consistent with Sabanayagam et. al.[11] who reported that increasing HbA1c categories had a higher prevalence of any retinopathy, mild retinopathy, moderate retinopathy, CKD, micro or macro-albuminuria and peripheral neuropathy. Another study[15] also found the similar association of HbA1c with retinopathy, nephropathy and neuropathy. Zoungas, et. al.[22] observed that for macrovascular events and death the apparent threshold of HbA1c level was 7.0%, and

for microvascular events the level was 6.5%. They also revealed that above thresholds, a higher level of HbA1c was significantly associated with higher risks of macrovascular, microvascular events and death in a log-linear manner. Below these thresholds, there was no significant relationship between mean HbA1c level and risks. In our study there were relatively few diabetic nephropathy events observed at HbA1c levels less than 7.0% so we could not properly evaluate the HbA1c levels below 7.0% in diabetic nephropathy.

Many previous studies[14,23,24] found that age was the single most important time related variable for renal impairment. Significant association of duration of diabetes and nephropathy was observed by Varghese, et. al.[24]. Like them we also found that advanced age and duration of diabetes were important risk factors for nephropathy. This study also revealed that lack of physical exercise was independent risk factors for nephropathy. It may be postulated that changed life style, food habit, less physical activity and stress may interfere with the metabolic process for glycaemic control and subsequent vascular complications[16-18]. In our study we found nephropathy significantly associated with not urban participants. We found a strong association of hypertension with nephropathy. Both systolic and diastolic blood pressures were significantly associated with diabetic nephropathy. Earlier, some studies[15,20] also observed the positive association of hypertension with nephropathy. Poor glycaemic control indicated by raised mean HbA1c, blood glucose levels in fasting and 2 hours after breakfast were significantly associated with increased prevalence of nephropathy in this study. These findings were consistent with other studies[15,25]. Viswanathan et. al.[25] found that the initial HbA1c along with initial systolic blood pressure was an important contributory factor for proteinuria. The strong relation of poor glycaemic control and nephropathy was also observed by Agrawal et. al.[15]. In this study we could not assess the urinary protein level of the participants because of our limitation. Proteinuria is an important contributing factor of nephropathy[14-18].

Conclusions

Our data from hospital based type 2 diabetic patients suggest that higher HbA1c levels >7% are significant risk factor of nephropathy and the risk increases markedly at HbA1c levels $\geq$ 8%. The prevalence and risk of diabetic nephropathy increased with advanced age, longer duration of diabetes, hypertension, poor glycaemic control, lacking of physical exercise etc. We should tightly control HbA1c and all other risk factors by appropriate preventive measures, so that the occurrence and worsening of diabetic nephropathy among type 2 diabetic patients could be prevented or atleast delayed.

Acknowledgements

This research was supported by Department of Biochemistry of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM). We are extremely grateful to Prof. Subhagata Choudhury, Director, Laboratory Services, BIRDEM for his assistance in implementing the study. It is our great pleasure to express our regards to all the staffs of blood collection rooms, biochemistry lab and library of BIRDEM for their endless support during the study period. Special thanks are extended to Prof. Dr. Md. Zulfiker Ali, Professor and HOD, Medicine & Gastroenterology, KYAMCH for revising and correcting the manuscript.

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