Original article

Association of Glycemic Control with Diabetic Nephropathy among Patients with Type 2 Diabetes Mellitus in Pakistan

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ABSTRACT

Background: Diabetic nephropathy is a common microvascular complication of diabetes mellitus and is a cause of significant morbidity and mortality. This study explores the relationship of HbA1c with diabetic nephropathy in Pakistani population.

Patients and methods: A cross-sectional study was conducted at the Internal Medicine Department of Shaikh Zayed Medical Complex (SZMC), Lahore, on patients with type 2 diabetes. Mean HbA1C levels were compared between patients with and without diabetic nephropathy by applying independent sample t-test, while suboptimal glycemic control was compared using chi-square test. Pearson's correlation was applied to assess the correlation of urinary albumin levels with duration of diabetes and HbA1c levels.

Results: A total of 80 patients with type 2 diabetes mellitus were included in the study. The mean age of all the participants was 47 $\pm$ 10 years. Out of these cases, 56.3% were male and 43.8% were female. Suboptimal glycemic control was present in 72.5% cases and 47.5% were diagnosed with diabetic nephropathy. Higher mean HbA1c levels were observed in the patients with nephropathy as compared to those without nephropathy (10.1 $\pm$ 1.1% vs 7.2 $\pm$ 0.8%, $p < 0.001$). All diabetic nephropathy cases (100%) had suboptimal glycemic control as compared to 47.6% of the cases without nephropathy ($p < 0.001$). The 24-hours urinary proteins had a strong correlation with HbA1c levels ($r = 0.771$, $p < 0.001$) and a moderate correlation with duration of diabetes ($r = 0.638$, $p <0.001$). In multivariate regression analysis, only obesity significantly predicted suboptimal glycemic control (OR: 4.346, 95% CI: 1.162 – 16.249, $p = 0.029$).

Conclusion: There is a significant association between diabetic nephropathy and suboptimal glycemic control. The urinary albumin levels have positive correlation with HbA1c levels and duration of diabetes. Obesity is a significant predictor of suboptimal glycemic control in Pakistani population. There is need to explore the factors contributing towards diabetic nephropathy in patients with diabetes.

Keywords:

Type 2 diabetes mellitus, Diabetic nephropathy, Diabetes complications, Glycemic control, Albuminuria

INTRODUCTION

Diabetic nephropathy is a common microvascular complication associated with diabetes mellitus and is responsible for significant morbidity and mortality. As the global burden of diabetes is on the rise, the significance of diabetic nephropathy as a public health concern is also increasing.[1]

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This deterioration of renal function has been estimated to occur in almost one-third of the cases of diabetes mellitus.[2] However, the development of nephropathy in patients with diabetes is an insidious process and may take years before kidney dysfunction begins to manifest. Diabetic nephropathy starts with asymptomatic microalbuminuria with incipient rise in systematic blood pressure. If undiagnosed and untreated at this level, this gradually leads to further renal damage and ultimately end stage renal disease (ESRD).[3] To prevent these grave complications, early detection of diabetic nephropathy is essential.[4]

Long-term glycemic control is a significant factor determining the development of both microvascular and macrovascular diabetic complications. This long-term control of diabetes is reflected by glycated hemoglobin (HbA1c) levels which represent average diabetic control over the last three months.[5] Studies have shown that HbA1c is a reliable predictor of development of diabetic microvascular, macrovascular, and autonomic complications.[6,7] Arnold et al. observed that in patients with HbA1c levels <5.7%, the mean time to development

of nephropathy was 15.9 years as compared to 8.3 years in those with HbA1C levels >8.5% ($p < 0.001$).[8]

The local data about association of diabetic nephropathy and HbA1c is interestingly heterogeneous. Studies by Qamar et al. and Jamil et al. showed a direct association between HbA1c levels and diabetes related nephropathy as depicted by both micro and macroalbuminuria.[9, 10] However, a study from Islamabad, Pakistan, published conflicting results about association of HbA1c levels with diabetic nephropathy.[11] Although, there is local data available on the association of HbA1c and diabetic nephropathy, but there are conflicting results available and the studies differ geographically and spatially with most of the studies being more than 5 years old. As the prevalence trends related to diabetes and its complications are evolving, it is essential to assess the recent trends and provide data for evidence informed decisions. Therefore, this study is designed to assess the relationship of HbA1c with diabetic nephropathy in Pakistani population. The results from this study will help in developing strategies from prevention and control of renal complications in patients with diabetes.

METHODS

A cross-sectional study was carried out at the Internal Medicine Department of Shaikh Zayed Medical Complex (SZMC), Lahore between 1st January, 2025 and 31st March, 2025. The approval for the study was taken from Research and Evaluation Unit (REU) of the College of Physicians and Surgeons, Pakistan (CPSP) (Ref # CPSP/REU/MED-2023-072-20999, dated 10th September, 2024). A non-probability consecutive sampling technique was employed and patients of age 35 to 70 years, either gender, and with diagnosis of Type 2 Diabetes mellitus were included in the study. Patients with less than one year duration of diabetes, hepatitis B or C, liver cirrhosis, pregnant females, gestational diabetes, or presenting with any acute infective illness were excluded from the study. A sample size of 80 patients was calculated by keeping confidence level of 95%, a margin of error of 8% and taking expected percentage of diabetic patients with nephropathy as 15.4% from study by Fares et al.[12] Patients were labeled as type 2 diabetes mellitus on the basis of one or both of the following: (i) fasting plasma glucose (FPG) level >126 mg/dl (7.0 mmol/L) and/or (ii) HbA1c > 6.5%.[13] Diabetic nephropathy was diagnosed by 24-hours urine albumin levels of more than 300 mg on two or more occasions separated at least by three months.[2] Diabetic control was labeled as "good glycemic control" (HbA1c < 7%) or "suboptimal glycemic control" (HbA1c > 7%).[14]

All patients were briefed about the study objectives and informed consent was taken. Sociodemographic data including age, gender, BMI, duration of diabetes, socioeconomic status, educational status, area of residence, and history of smoking was recorded. A 5-ml venous blood sample was drawn and sent for HbA1c levels. Patients were managed according to standard protocols under the supervision of consultant physicians and nephrologists. Data from the data collection proformas was entered in to Microsoft Excel spread sheets and then transferred and analyzed through IBM SPSS Statistics software version 27.0. Descriptive statistics were presented as mean ± standard deviation (SD) for quantitative variables, and as frequencies and percentages for qualitative variables. Mean HbA1c levels were compared between patients with and without diabetic nephropathy using the independent-samples t-test, while suboptimal glycemic control was compared using the chi-square test. The correlation of urinary albumin levels with duration of diabetes and HbA1c levels was assessed using Pearson's correlation coefficient. A correlation coefficient of <0.40 was considered a weak correlation, 0.40–0.69 a moderate correlation, and ≥0.70 a strong correlation.[15] Univariate and multivariate logistic regression analyses were performed, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the association of various sociodemographic and clinical variables with suboptimal glycemic control. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 80 cases with type 2 diabetes were included in the study. The mean age of all the participants was 47 $\pm$ 10 years. Out of these 80 cases, there were 45 (56.3%) males and 35 (43.8%) females. The mean duration of diabetes was 10 $\pm$ 5 years. The baseline characteristics of study participants are given in table 1. The mean 24-hours urinary proteins levels were 233 $\pm$ 116 mg and diabetic nephropathy was labeled in 38 (47.5%) cases. The mean HbA1c was 8.6 $\pm$ 1.8% and good glycemic control was present in 22 (27.5%) and suboptimal glycemic control in 58 (72.5%). The clinical outcomes of the study are given in table 2.

The mean HbA1c levels in cases with nephropathy were significantly higher than those without nephropathy (10.1 $\pm$ 1.1% vs 7.2 $\pm$ 0.8%, $p < 0.001$). All patients with nephropathy (100%) had suboptimal glycemic control as compared to 47.6% of those without nephropathy ($p < 0.001$). The comparison of glycemic control between diabetic patients with and without nephropathy is given in table 3. There was a strong correlation between HbA1c levels and 24-hours urinary proteins ($r = 0.771$, $p < 0.001$). A moderate correlation was observed between duration of diabetes and 24 hours urinary proteins ($r = 0.638$, $p < 0.001$). Figure 1 ('a' and 'b') shows the correlation of

24hours urinary proteins with HbA1c and duration of diabetes.

Results from univariate logistic regression analysis showed that age >50 years (OR: 4.471, 95% CI: 1.188 – 16.820, p = 0.027), obesity (OR: 5.829, 95% CI: 1.877 – 18.099, p = 0.002), low monthly income (OR: 3.904, 95% CI: 1.270 – 11.997, p = 0.017), lower educational status (OR: 7.364, 95% CI: 2.204 – 24.602, p = 0.001), rural residence (OR: 8.707, 95% CI: 1.083 – 69.993, p = 0.042), smoking (OR: 4.471, 95% CI: 1.188–16.820, p = 0.027), and diabetes duration >10 years (OR: 9.333, 95% CI: 1.997–43.627, p = 0.005) were significant predictors of suboptimal diabetic control, while gender (p = 0.489) had no significant effect. In multivariate regression analysis, only obesity significantly predicted suboptimal control (OR: 4.346, 95% CI: 1.162 – 16.249, p = 0.029). Other variables such as age (p = 0.897), gender (p = 0.448), monthly income (p = 0.375), educational status (p = 0.336), residence (p = 0.332), smoking (p = 0.828), and duration of diabetes (p = 0.127) did not show significant association. Univariate and multivariate regression analysis showing association of various demographic and clinical variables with suboptimal glycemic control is given in Table 4.

Table 1: Baseline characteristics of the study population (N = 80)

Characteristic	**Mean**	**S.D**	**Minimum**	**Maximum**
Age (years)	47	10	32	75
BMI (Kg/m^2)	29.4	1.6	25.0	32.0
Duration of DM (years)	10	5	2	23
Characteristic			**Frequency (n)**	**Percentage (%)**
Gender	Male		45	56.3%
	Female		35	43.8%
Socio-economic status	Low		36	45.0%
	Middle		40	50.0%
	High		4	5.0%
Educational status	Illiterate		11	13.8%
	Primary		29	36.3%
	Middle		23	28.7%
	Matric and Above		17	21.3%
Residence	Urban		15	18.8%
	Peri urban		47	58.8%
	Rural		18	22.5%
Smoking	Present		27	33.8%
	Absent		53	66.3%

Table 2: Clinical outcomes of study population (N = 80)

Outcome	**Mean**	**S.D**	**Minimum**	**Maximum**
24-hr urinary proteins (mg)	233	116	0	400
HbA1c (%)	8.6	1.8	6.2	12.5
Outcome			**Frequency (n)**	**Percentage (%)**
Diabetic Nephropathy		Present	38	47.5%
		Absent	42	52.5%
Diabetic control	HbA1c < 7		22	27.5%
	HbA1c > 7		58	72.5%

Table 3: Comparison of diabetic control between diabetic patients with and without nephropathy (N = 80)

Characteristic	**Diabetic Nephropathy**				**p - value**
	Present (n = 38)		**Absent (n = 42)**		
	Mean	S.D	Mean	S.D	
HbA1c	10.1	1.1	7.2	0.8	< 0.001$^{\dagger *}$
	Frequency (n)	**Percentage (%)**	**Frequency (n)**	**Percentage (%)**	p - value
HbA1c < 7	0	0.0%	22	52.4%	< 0.001$^{\alpha *}$
HbA1c > 7	38	100.0%	20	47.6%	

$^{\alpha}$T-test was applied to compare mean values

†Chi-square test was applied

*p-value < 0.05 was considered significant

Table 4: Logistic Regression analysis showing association of various demographic and clinical factors with diabetic control (N = 80)

Factors	Univariate		Multivariate	
	OR (95% CI)	p - value	OR (95% CI)	p - value
Age				
< 50 years	–		–	
> 50 years	4.471 (1.188 – 16.820)	0.027*	0.869 (0.104 - 7.252)	0.897
Gender				
Female	–		–	
Male	1.417 (0.529 – 3.796)	0.489	1.639 (0.4576 - 5.875)	0.448
Obesity (BMI > 30 Kg/m^2)				
Non-obese	–		–	
Obese	5.829 (1.877 – 18.099)	0.002*	4.346 (1.162 - 16.249)	0.029*
Monthly Income (PKR)	–		–	
< 50k per month > 50k per month	3.904 (1.270 – 11.997)	0.017*	1.962 (0.442 - 8.697)	0.375
Educational status				
Middle or higher	–		–	
Primary or no education	7.364 (2.204 – 24.602)	0.001*	2.0807 (0.467 - 9.258)	0.336
Residence				
Urban/peri-urban	–		–	
Rural	8.707 (1.083 – 69.993)	0.042*	3.485 (0.279 - 43.538)	0.332
Smoking				
Non-smoker	–		–	
Smoker	4.471 (1.188 – 16.820)	0.027*	1.218 (0.205 - 7.237)	0.828
Diabetes duration				
< 10 years	–		–	
> 10 years	9.333 (1.997 – 43.627)	0.005*	5.228 (0.6258 - 43.675)	0.127

Abbreviations: OR = odds ratio, **CI** = Confidence Interval
*Statistically significant p – value of < 0.05

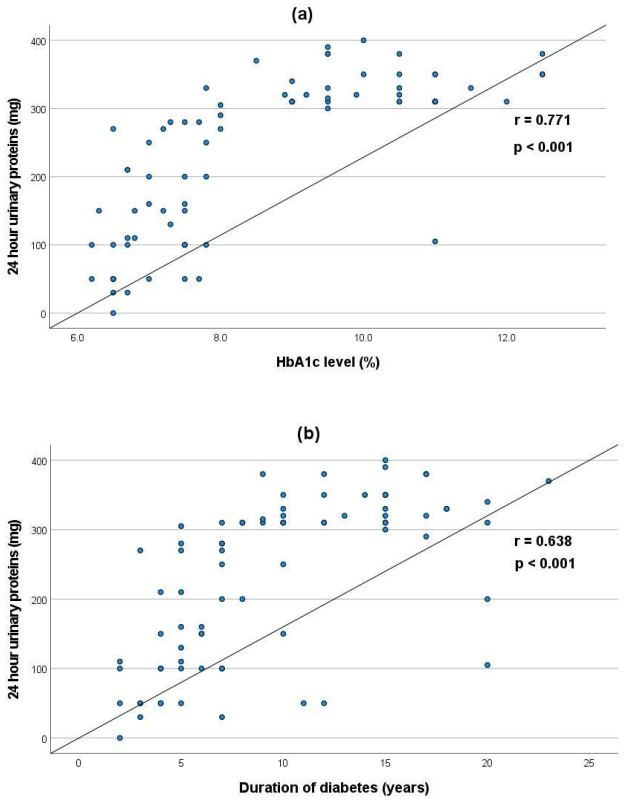

Figure 1: (a and b): Correlation between 24-hours urinary proteins and (a) HbA1c and (b) duration of diabetes (N = 80)

DISCUSSION

The present study was designed to evaluate the frequency of diabetic nephropathy in patients with diabetes and its association with glycemic control. The results showed the prevalence of diabetic nephropathy as 47.5%. A wide variation in prevalence of diabetic nephropathy has been reported in various local studies. One of the highest prevalence was observed in a local study conducted at Fatima Memorial Hospital, Lahore, by Munir et al., in which 88% of the patients had albuminuria. Using serum creatinine as a marker showed that 93% of patients had nephropathy.[16] On the contrary, a local study from Hyderabad by Iqbal et al. showed the prevalence of diabetic nephropathy to be only 46%.[17] Although there are variations in these results, yet these results point towards a high prevalence of nephropathy in Pakistani diabetic population as compared to global trends. A systematic review of twenty studies from thirteen different countries showed an overall prevalence of 27%.[18] The high prevalence of diabetic nephropathy in Pakistani population can be attributed to a number of causes such as suboptimal glycemic control, high prevalence of other related conditions such as hypertension, lack of knowledge and awareness regarding diabetic complications, and limited access nephrology services.[19, 20] In addition to these factors, genetics also play a significant role in development of diabetes and its complications and can be regarded as one of the main factors contributing to nephropathy.[21]

In the present study, only 27.5% of the patients with diabetes had good glycemic control while 72.5% showed suboptimal glycemic control. Similar results were observed in a systematic review of studies on Pakistani patients with diabetes, where 44.7% to 86.4% of the patients practiced suboptimal glycemic control.[22] Large scale data from the United States (US) has shown that within the years 2013 – 2023 the diabetic control rate among the US population ranged from 43.5% to 54.3%.[23] Studies from lower middle income countries (LMICs) from South Asia and parts of Africa have shown higher incidence of suboptimal glycemic control in range similar to that observed in the present study.[24, 25] The present study reported a strong association between diabetic nephropathy and suboptimal glycemic control. All the patients with diabetic nephropathy had suboptimal glycemic control as compared to 47.6% of the diabetic patients without nephropathy ($p < 0.001$). Similar results were reported in a local study by Ali et al. in which 100% of the patients with nephropathy had suboptimal glycemic control as compared to 40.5% of the patients without nephropathy.[26]

A strong positive correlation was reported between HbA1c levels and 24-hours urinary proteins in the present study ($r = 0.771$, $p < 0.001$). In a previous study by Qamar et al., HbA1c levels were found to be correlated with albuminuria. A moderate correlation of 0.659 was observed which is close to that observed in the present study.[9] Another local study from Rahim Yar Khan showed that raised HbA1c was significantly associated with microalbuminuria ($p < 0.001$).[27] However, in a study from Eastern Finland, no significant association of HbA1c was observed with albuminuria in patients with type 2 diabetes ($p = 0.085$). Interestingly, other glycemic parameters such as 1-hour blood glucose levels ($p = 0.001$) and 2-hour blood glucose levels ($p = 0.015$) showed significant association with albuminuria. Also the HbA1c cutoff of 6.5% for defining suboptimal glycemic control was less than that used in the present study.[28] These findings suggest that estimation of association of glycemic control with diabetic nephropathy is influenced by the parameter used and its cutoff for determining suboptimal control. Nevertheless, literature is evident on the role of suboptimal glycemic control in causing albuminuria. The effect of advanced glycation end products (AGEs) on glomerular basement membrane, glomerular hyperfiltration due to hyperglycemia, and direct effect of oxidative stress and inflammation on mitochondrial dysfunction, endothelium and podocytes damage, and mesangial expansion are some of the complex pathologies involved in the disease process.[29, 30]

The variation in the results of the different studies on the extent of association of suboptimal glycemic control with diabetic nephropathy can be explained by delving deep in to the pathophysiological basis of this association. Various factors that can influence this association include phenotypic differences such as non-albuminuric diabetic kidney disease which is primarily caused by hypertension and atherosclerosis, masking effect of various drugs such as inhibitors of Sodium glucose Cotransporter-2 (SGLT2) and Renin-Angiotensin-Aldosterone System (RAAS), various statins, and glycemic variability and postprandial spikes that are not accounted for merely by HbA1c levels.[31-34] Also newer drugs such as SGLT2, glucagon-like peptide-1 (GLP-1) inhibitors, and non-steroidal mineralocorticoid receptor antagonists can prevent or delay the development of diabetic nephropathy.[35,36] Genetic predisposition, particularly in Asian population, entails that suboptimal glycemic control has a greater effect on albuminuria as compared to other populations.[37]

All these factors collectively influence the association of suboptimal glycemic control with albuminuria and explain the variability observed in the present study and various other studies. Nevertheless, albuminuria has been shown to precede the development of diabetes. In cases with pre-diabetes a urinary albumin creatinine ratio (UACR) > 30 mg/g can be a predicted for diabetes.[38] Appearance of urinary podocytes mRNA before development of microalbuminuria is also an indication that renal structural changes begin to occur well before the development of albuminuria is pre-diabetic patients.[39]

Another significant finding from the present study was the moderate positive correlation between duration of diabetes and 24-hours urinary proteins ($r = 0.638$, $p < 0.001$). In the study by Asghar et al., the duration of diabetes was significantly longer in cases with albuminuria ($p = 0.04$), thus pointing towards a significant association of diabetes duration with renal complications.[27] In contrast to the findings of the present study, a weak correlations between urinary albumin creatinine ratio (UACR) and duration of diabetes ($r = 0.183$, p 0.035) was observed in a local study by Sana et al.[40] However, literature is evident on the detrimental effects of long standing diabetes on renal function. Jin et al. showed that glomerular filtration rate (GFR) was negatively correlated with duration of diabetes ($r = - 0.149$, $p < 0.001$), which implies that longer duration of diabetes results in decrease in renal function.[41] The cumulative glycemic exposure and microvascular injury due to long standing diabetes are the reasons for renal dysfunction.[42] The epigenetic and metabolic memory after periods of suboptimal glycemic control sustains the activation of inflammatory pathogenic pathways long after diabetic control has been improved.[43] In addition to these factors,

the interaction of poorly controlled diabetes with other comorbidities such as hypertension, obesity, and dyslipidemia provides a synergistic effect to accelerate kidney dysfunction.[44]

Results of univariate regression analysis showed that age >50 years (p = 0.027), obesity (p = 0.002), low monthly income (p = 0.017), lower educational status (p = 0.001), rural residence (p = 0.042), smoking (p = 0.027), and diabetes duration >10 years (p = 0.005) were significant predictors of suboptimal diabetic control. In multivariate regression analysis, only obesity significantly predicted suboptimal control (p = 0.029) thus confirming its role as a marker of inadequate metabolic control. These findings highlight the need for intensified monitoring and tailored interventions in patients with nephropathy to improve glycemic outcomes. A local study from Bahawalpur, Pakistan, by Ali et al. showed that raised BMI, urban residence, illiteracy, and long standing diabetes are significant predictors of suboptimal glycemic control.[45] Certain other factors including age < 65 years, physical inactivity, non-adherence to medication, and presence of other comorbidities were reported to significantly predict suboptimal glycemic control in an Ethiopian study by Legese et al.[46] A systematic review of studies from nine different countries showed that a number of factors including age, gender, cigarette smoking, physical activity, obesity, hypertension, asthma, and compliance to anti-diabetic treatment were associated with glycemic control.[47] Thus, glycemic control in patients with diabetes appears to be multifactorial and a detailed discussion on these factors cannot be encompassed in this study. The present study has highlighted some common factors and the authors recommend further studies to explore the factors contributing to suboptimal glycemic control in patients with diabetes.

The authors acknowledge various limitations of the present study. This study was conducted at a single-center study in a tertiary care hospital of a metropolitan city, therefore, the results cannot be generalized over patients with diabetes presenting in other parts of the country. The study has a modest samples size which may raise the concern regarding inadequacy of estimation of the association of suboptimal glycemic control with nephropathy.[48] The authors also acknowledge the inherent weakness of the cross-sectional study design for determination of causality in contrast to other association specific study designs.[49] The authors, therefore, recommend further large scale, multi-centric studies based on association study designs to provide better understanding of the relationship between glycemic control and renal dysfunction. Qualitative studies exploring the factors responsible for suboptimal glycemic control in our population will provide an in-depth analysis of the situation and give valuable insights for further research and policy making.

CONCLUSION

Based on the results of this study it is concluded that the diabetic population of Pakistan has a high prevalence of nephropathy. Majority of the patients have suboptimal glycemic control and there is a significant correlation between diabetic nephropathy and suboptimal glycemic control. The urinary albumin levels significantly correlate with HbA1c levels and duration of diabetes. Obesity is a significant predictor of suboptimal glycemic control in Pakistani population. There is need to explore the factors that contributing towards diabetic nephropathy in patients with diabetes in order to understand the complex mechanisms determining its pathogenesis and to provide evidence for formulating nationwide strategies to counter the high prevalence of diabetic nephropathy in Pakistani population.

Author Contributions

Dr. Hafiz Muhammad Umar Masood: Conception and design, analysis and interpretation of data, drafting the article, critical revision for important intellectual content, and final approval

Dr. Muhammad Uthman: Conception and design, analysis and interpretation of data.

Dr. Uzma Iqbal: Analysis and interpretation of data, and drafting the article.

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