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ORIGINAL ARTICLE

Association between microvascular complications and chronic kidney disease stages in type 2 diabetic patients

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ABSTRACT

Background: Rapid urbanization and lifestyle changes have led to a surge in type 2 diabetes mellitus (T2DM) rates and its microvascular complications.

Objective: : To assess the association between microvascular complications and the stages of chronic kidney disease (CKD) in patients with type 2 diabetes mellitus and to compare HbA1c levels across the different stages of CKD.

Methods: It was a cross sectional descriptive study conducted from 27th October 2022 to 26th April 2023 at outpatient Department of Nephrology, Liaquat University of Medical & Health Sciences (LUMHS), Jamshoro, Sindh, Pakistan. Data was collected after approval from the Ethical Research Committee (LUMHS/REC/-243). Informed consent was obtained from 136 patients, males and females, 45 to 65 years of age, type 2 diabetics (for more than 10 years) with diagnosed CKD. The modification of diet in renal disease (MDRD) formula was used to estimate eGFR for chronic kidney disease staging. Diabetic retinopathy was diagnosed using fundoscopic examination and diabetic neuropathy was confirmed by symptoms and positive signs on examination. Data analysis was performed using SPSS version 22. A p-value of ≤ 0.05 was deemed statistically significant.

Results: Out of 136 patients, 75 (55.15%) were males and 61 (44.85%) were females. Mean age, eGFR, HbA1c, and duration of diabetes were 53.27 ±6.39 years, 54.55±27.26 mL/min/1.73 m², 9.02±1.67% and 14.06±4.05 years. The analysis showed that 8.1%, 40.4%, 22.05%, 22.05%, and 7.4% of patients were in CKD stages 1, 2, 3, 4, and 5, respectively. There was a significant association between diabetic microvascular complications, retinopathy and neuropathy, and the stages of CKD ($p<0.05$).

Conclusion: There is an association between microvascular complications i.e. neuropathy and retinopathy and the stages of CKD in type 2 diabetic patients. Additionally, HbA1c levels varied across CKD stages, highlighting the relationship between glycemic control and kidney function.

Key Words: Diabetes mellitus, Estimated glomerular filtration rate, Chronic kidney disease, Microvascular complications

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INTRODUCTION

Diabetes Mellitus (DM) impacts 537 million people globally with Pakistan ranked among the nations with the highest prevalence rates.[1] According to the latest International Diabetes Federation Atlas, around 33 million people are affected by type 2 diabetes mellitus (T2DM) in Pakistan.[2] Furthermore, in Pakistan, about 8.9 million individuals with diabetes remain undiagnosed, while another 11 million have impaired glucose tolerance.[3]

DM leads to both microvascular and macrovascular complications. In T2DM, the prolonged pre-symptomatic phase often lasting several years heightens the risk of developing these complications.[4]

Among the most significant microvascular complications are diabetic retinopathy, neuropathy, and nephropathy.[5] Diabetic nephropathy, in particular, is a leading cause of developing end-stage renal disease (ESRD), significantly increasing healthcare costs and patient burden.[6] Approximately, 40% of diabetics acquire CKD over their lifespan.[7] Microalbuminuria and estimated glomerular filtration rate (eGFR) are the clinically significant markers for the evaluation of renal function. eGFR is an important indicator of kidney function that decreases as diabetic nephropathy advances.[8] Monitoring eGFR in conjunction with glycated hemoglobin (HbA1c), a long-term measure of blood glucose levels, may provide insight into the interrelationships between hyperglycemia and renal function in type 2 diabetes.[9] Elevated HbA1c levels are also associated with an increased risk of microvascular complications.[10]

Studies have also shown that a decreased eGFR predicts not just impaired renal function but also other diabetes-related problems such as diabetic neuropathy and diabetic retinopathy.[11,12] This makes evaluating eGFR in diabetes individuals critical. However, little information is presently available about how the presence of one microvascular complication influences the chance of acquiring another microvascular complication. Despite the established role of CKD staging in clinical management, there is a limited local literature exploring its relevance to the microvascular complications in T2DM, such as diabetic retinopathy and neuropathy. Understanding these associations is important for identifying high-risk patients, improving prognostic assessments, and optimizing therapeutic strategies. Therefore, we assessed the association between microvascular complications and the stages of CKD in patients with T2DM and compared HbA1c levels across the different CKD stages.

METHODS

This cross-sectional study was conducted from 27th October 2022 to 26th April 2023 at outpatient Department of Nephrology at Liaquat University Hospital in Jamshoro, Sindh, Pakistan. A sample size of 136 was calculated based on a 22.5% frequency of neuropathy as a microvascular complication in patients with T2DM, [4] 7% margin of error, and 95 % confidence level. The non-probability consecutive sampling technique was used and informed consent was taken from the participants.

The study included 136 cases of T2DM (having T2DM for more than 10 years) with diagnosed CKD (patients with albuminuria or glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 and persisting for ≥ 3 months), 45 to 65 years of age, both the males and females. Pregnant and breast feeding subjects, having connective tissue abnormalities, or chronic liver illness were excluded. The Modification of Diet in Renal Disease (MDRD) formula was used to calculate eGFR which was used to classify CKD into five stages. Patients were categorized as stage 1 (eGFR ≥ 90 ml/min/1.73 m²), stage 2 (eGFR 60 - 89 ml/min/1.73 m²), stage 3 (eGFR 30 - 59 ml/min/1.73 m²), stage 4 (eGFR 15 - 29 ml/min/1.73 m²), and stage 5 (eGFR less than 15 ml/min/1.73m²).[5] The diabetic retinopathy was diagnosed on fundoscopic examination. Diabetic neuropathy was diagnosed based on the presence of neuropathy symptoms and at least one positive sign on examination, such as loss of ankle reflex, vibration sense, pressure sense, pain sensation, or temperature sensation.

Ethical Approval

Ethical approval from the Ethical Research Committee of Liaquat University of Medical & Health Sciences, Jamshoro, Sindh, Pakistan (LUMHS/REC/-243) was received on December 16, 2021.

Statistical Analysis

Data analysis was performed using SPSS version 22. Categorical variables were expressed as frequencies and percentages, while numerical variables were presented as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was used to compare HbA1c levels across various stages of CKD. Chi-square and Fisher's Exact tests were used to find out the association between microvascular complication and CKD stages. A p-value of ≤ 0.05 was deemed statistically significant.

RESULTS

Out of 136 patients, 75 (55.15%) were males and 61 (44.85%) were females. The mean ± SD values of age, eGFR, HbA1c, and duration of diabetes are shown in Table 1.

According to CKD stages, among 136 patients, 11 patients (8.1%) were in stage 01, 55 patients (40.4%)

in stage 2, 30 patients (22.05%) in stage 3, 30 (22.05%) were in stage 4, and 10 patients (7.4%) in stage 5. Frequencies of microvascular complications among the study participants are shown in Table 2.

Table 1: Baseline characteristics of the study population

Variable	Mean ± SD (n=136)
Age (years)	53.27±6.39
eGFR (ml/min/1.73m^2)	54.55±27.26
HbA1c (%)	9.02±1.67
Duration of diabetes (years)	14.06±4.05

A significant association was found between microvascular complications i.e. retinopathy and neuropathy and stages of CKD with increased frequency in CKD stages 3, 4 & 5 (p-value=0.000) as shown in Table 3. There was a significant difference in HbA1c levels among the five groups (Table 3). In the post hoc analysis of HbA1c levels across CKD stages, a significant difference was observed between CKD stage 3 and CKD stage 5 (p = 0.016). This suggests that as the severity of CKD increases, there may be a corresponding change in HbA1c levels. These findings highlight the importance of closely monitoring glycemic control in patients with advanced stages of CKD.

Table 2: Frequencies of microvascular complications in the study participants

Complications	n	%
Retinopathy		
Yes	77	56.6
No	59	43.4
Neuropathy		
Yes	67	49.3
No	69	50.7
Hypertension		
Yes	94	69.1
No	42	30.9
Smoking		
Yes	47	34.6
No	89	65.4

Table 3: Distribution of clinical variables across chronic kidney disease stages

Variable		Stage 1 (n=11)	Stage 2 (n=55)	Stage 3 (n=30)	Stage 4 (n=30)	Stage 5 (n=10)	p-value
HbA1c %		**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	
		8.66±1.17	8.93±1.42	9.64±1.97	9.11±1.78	7.76±1.40	0.028*[a]
		n(%)	**n(%)**	**n(%)**	**n(%)**	**n(%)**	
Retinopathy	Yes	1(9.1)	7(12.7)	30(100)	29(96.7)	10(100)	
	No	10(90.9)	48(87.3)	0(0)	1(3.3)	0(0)	0.000*[b]
Neuropathy	Yes	1(9.1)	5(9.1)	23(76.7)	28(93.3)	10(100)	
	No	10(90.9)	50(90.9)	7(23.3)	2(6.7)	0(0)	0.000*[b]
Hypertension	Yes	6(54.5)	41(74.5)	21(70)	20(66.7)	6(60)	
	No	5(45.5)	14(25.5)	9(30)	10(33.3)	4(40)	0.674[c]
Smoking	Yes	0(0)	18(32.7)	15(50%)	10(33.3)	4(40)	
	No	10(100)	37(67.3)	15(50%)	20(66.7)	6(60)	0.56 [b]

*[a]One-way ANOVA was applied, [b]Fisher's Exact test was applied, [c]Chi Square test was applied, Tests were applied on n=136. *p-value of ≤ 0.05 is statistically significant.*

DISCUSSION

The findings of this study provide valuable insights into the association pattern between CKD stages, microvascular complications and HbA1c levels, highlighting the interplay between the renal function, glycemic control, and microvascular complications in patients with T2DM.

In the present study, the majority of patients were in CKD stage 2, which shows that CKD is frequently underdiagnosed until it reaches this stage and this is due to the absence of symptoms in the early stage. Recognizing and controlling CKD in early stages can help lower the likelihood of the disease progressing to more severe stages.[13] In a study of 5000 people with type 2 diabetes, Kong et al. reported that 37.5% had stage 2 CKD and 15.8% had stage 3 CKD, emphasizing the close link between diabetes and renal impairment.[14] Jelinek et al. established a connection between effective glycemic control and a reduced incidence of micro- and macrovascular complications in individuals with T2DM.[15] Chia et al. also highlighted that variability in HbA1c is an independent risk factor for the progression of renal dysfunction.[16] We observed low levels of HbA1c in the CKD stage 5, indicative of functional renal failure, a progressive functional loss, commonly seen in CKD among T2DM patients. Similarly, Kuo et al. demonstrated that higher HbA1c levels are observed at earlier CKD stages.[17]

The association between diabetic retinopathy and kidney function has been widely reported. According to studies, people who have diabetic retinopathy are more likely to acquire kidney disease, particularly diabetic nephropathy. Microvascular abnormalities in the retina are indicative of generalized microvascular damage that may also be present in other organs, including the kidneys.[18] Grunwald et al. found that the existence of the intraretinal microvascular abnormalities in diabetic patients is related to the increased risk of nephropathy, even in the absence of overt proteinuria.[19] This link is thought to be caused by common pathophysiological mechanisms such as endothelial dysfunction, hyperglycemia-induced vascular damage, and inflammation; all of which affect the microvasculature of the retina and kidney. Similarly, our findings also revealed significant association between diabetic retinopathy and CKD stages.

Several previous studies have shown a link between lower eGFR and the development of diabetic neuropathy.[20,21] We observed that patients in CKD stage 5 were more likely to have diabetic neuropathy compared to those in earlier CKD stages. A study conducted by Zhang et al. established a robust and significant correlation between lower eGFR and the presence of diabetic neuropathy.[22]

Our study looked into the link between hypertension and the stage of CKD in diabetic patients. Interestingly, our findings revealed no significant relationship between hypertension and the severity of CKD defined by the stage of renal impairment. This conclusion contradicts much of the previous literature, which links hypertension to the progression of CKD, particularly in diabetics.[23] The Framingham Heart Study and other studies have found that elevated blood pressure promotes kidney disease in diabetes by boosting both hemodynamic and non-hemodynamic kidney damage.[24]

Existing research supports the concept that smoking is a substantial risk factor for the advancement of CKD in the diabetic population. Smoking has also been linked to the development of diabetic nephropathy, a major complication in the diabetic kidney disease continuum, by exacerbating the effects of hyperglycemia and hypertension, the two most prominent causes of renal damage in diabetes. Furthermore, a study has reported that smoking significantly raised the risk of ESRD in diabetic individuals, highlighting smoking's role as a potent modulator of kidney disease development.[25]

Our study found no significant association between smoking and the stage of CKD in the diabetic patients, despite the abundance of data that smoking is associated with worse renal outcomes in diabetes.

CONCLUSION

In this study, there is a significant association between microvascular complications, diabetic neuropathy and retinopathy, and the stages of chronic kidney disease. Moreover, the significant difference in HbA1c levels across the various chronic kidney disease stages indicates the relationship between glycemic control and kidney function. These results underscore the need for careful monitoring of microvascular complications in the management of patients with diabetes and chronic kidney disease.

Limitations of the study

This study is observational and cannot establish causality. Other factors, such as hypertension may

also contribute to the renal impairment and microvascular complications.

Future Recommendations

Prospective studies and clinical trials are needed to further investigate these relationships and determine the cause-and-effect relationships.

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RV: Conception of the study, data collection, manuscript drafting, approval of final version to be published

MK: Data analysis & interpretation, manuscript drafting, approval of final version to be published

PM: Data acquisition, manuscript drafting, critical review, approval of final version to be published

SG: Data collection, data analysis, critical review, approval of final version to be published

All Authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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