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RESEARCH ARTICLE

HbA1c AND Spot Urine Protein Creatinine Ratio as Predictors of Progression of Diabetic Nephropathy in Type 2 Diabetes Mellitus Patients in Rural Tertiary Care Teaching Hospital

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Abstract: ***Background and Objectives***Diabetes Mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative insulin deficiency. The International Diabetes Federation projected that there will be 642 million diabetics by 2040. India is the diabetes capital of the world. Diabetic nephropathy is the leading cause of end stage renal disease. Proteinuria is an early marker of reversible nephropathy and a predictor of end organ damage.Relation between hyperglycemia and proteinuria is not linear. HbA1c of 8.1% is a threshold above which risk of proteinuria increases logarithmically. Achieving the best metabolic control (HbA1c <7%) is an effective strategy for delaying the progression to advanced stages of nephropathy. Hence, this study was conducted with the objective to determine HbA1C and spot Urine PCR as predictors of progression of Diabetic Nephropathy in Type 2 DM patients at Rural Tertiary care Hospital especially in an outpatient setting. ***Methods***In the present study, a total of 100 patients were considered, 50 patients were having HbA1C levels of more than or equal to 7 (Group A) and 50 patients were having HbA1C levels less than 7 (group B). Spot Urine protein creatinine ratio and HbA1c were done and correlated in each group. ***Results*** There was a significant correlation of Hba1C with spot urine protein creatinine ratio and there is significant association of them with Proteinuria, duration of diabetes, diabetic retinopathy.***Conclusion:*** There is a positive correlation of HbA1C with spot protein creatinine ratio and there is a significant association of glycated hemoglobin level with the amount of proteinuria, which is an early predictor of progression to Diabetic Nephropathy.

Keywords: **Angiotensin Converting Enzyme; Adenosine Triphosphate; End stage Renal Disease; Diabetic Retinopathy; Hemoglobin A1c (Glycated hemoglobin); Spot Protein Creatinine Ratio; Transforming Growth Factor; Sodium Glucose co transporter-2 inhibitors.**

INTRODUCTION

Diabetes Mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin.1 Diabetes mellitus more simply called as diabetes, is a serious, long term (or “chronic”) condition that occurs when raised levels of blood glucose occur because the body cannot produce any or enough of the hormone insulin or cannot effectively use the insulin it produces.2 Diabetes mellitus (DM) has reached epidemic proportions globally.3 The World Health Organization (WHO) estimated that there were 135 million diabetic individuals in the year 1995 and it has been projected that this number will increase to 300 million by the year 2025.4 India is often referred to as the ‘Diabetes capital of the world’, as it accounts for 17% of the total number of diabetes patients in the world.5

Diabetic nephropathy (DN) is the leading cause of chronic kidney disease and end stage renal disease worldwide.5 It develops in 40% of patients with type 2 diabetes mellitus and 30% of patients with Type 1 diabetes mellitus. Proteinuria is recognized as an independent risk factor for cardiovascular and renal disease and as a predictor of end organ damage.6 In particular, detection of an increase in protein excretion is known to have both diagnostic and prognostic value in the initial detection and confirmation of renal disease.7 24-hour urine collection is the gold standard to measure proteinuria. However, in clinical practice 24-hour urine collection is cumbersome and also errors in the collection are seen in 10-20% of samples8 making it an unreliable measure of proteinuria. To circumvent this problem, Ginsberg et al.,9 proposed measurement of protein to creatinine ratio (PCR) in a spot urine (SpUr) sample to predict 24-hour proteinuria. Creatinine excretion is variable within individuals and largely depends on muscle mass, which is influenced by several factors such as age, gender, body size, and diet. [10,11] Creatinine excretion in healthy as well as CKD populations of South Indian rural patients is unexplored and hence spot urine protein creatinine ratio (SpUr-PCR) to measure proteinuria remains unevaluated in them. Proteinuria is an early marker of reversible nephropathy and can spot glomerular disease

in its very early stages. Tests for protein excretion in the urine are necessary for the early diagnosis of diabetic nephropathy.12

HbA1c of 8.1% (average blood glucose 200mg/dl) is a threshold above which risk of proteinuria increases logarithmically.13 Long duration of diabetes, poor glycemic control, elevated blood pressure, dyslipidemia, presence of diabetic retinopathy are important initiators as well as accelerators for the progression of diabetic nephropathy.14 Achieving the best metabolic control (HbA1c <7%), treating hypertension (130/80 mmHg or 125/75 mmHg if proteinuria 1g/24 hour), and treating dyslipidemia (LDL cholesterol 100 mg/dl) are effective strategies for delaying the progression to more advanced stages of nephropathy and in reducing cardiovascular mortality in patients with and type 2 diabetes.15 Hence, this study was conducted with the objective to determine HbA1C and spot Urine PCR as predictors of progression of Diabetic Nephropathy in Type 2 DM patients at Rural Tertiary care Hospital especially in an outpatient setting.

MATERIAL AND METHOD

The hospital-based observational study was conducted over 18 months at Adichunchanagiri Hospital and Research Centre, B.G. Nagara, in the Department of Medicine, involving Type 2 diabetic patients attending the hospital. The study included participants aged over 18 years, both known and newly diagnosed cases of Type 2 Diabetes Mellitus, who provided informed consent. Patients were excluded if they had acute febrile illnesses, malignancies, collagen vascular disorders, systemic conditions causing proteinuria, drug-induced proteinuria, nephrotic range proteinuria, pregnancy, hypertension, hemochromatosis, hypothyroidism, iron deficiency anemia, hemolytic anemia, hemoglobinopathies, chronic alcoholism, chronic inflammatory conditions, chronic liver disease, or conditions contributing to chronic kidney disease other than T2DM.

Based on the study conducted by Juhi Aggarwal16 et al in Rural India (Uttar Pradesh), the prevalence of Proteinuria in type 2 diabetes mellitus patients is 52.04%. Sample size calculated using the formula- n = (z)2 p(1-p) / d2, where z = level of confidence according to the standard normal distribution (For level of confidence of 95%, z = 1.96) and absolute precision at 10%, sample size of 96 was obtained and rounded off to 100.

Data collection involved detailed history taking, clinical evaluation, physical examination, and structured investigations of the first 100 subjects presenting with Type 2 Diabetes Mellitus, following ethical clearance and informed consent. Investigations performed included fasting plasma glucose, postprandial blood sugar, glycated hemoglobin (HbA1c), spot urine protein-creatinine ratio, serum creatinine, blood urea, urine routine, complete hemogram, fundoscopy, and additional tests like liver function tests, fasting lipid profile, ultrasound, CT scan, or MRI when necessary. Spot urine samples (Single voided urine) were collected in sterile containers and analyzed in the biochemistry lab using immunoturbidimetric methods for urine protein and modified Jaffe's reaction for urine creatinine, both performed on automated analyzers. The protein-creatinine ratio was calculated and expressed in mg/g. Venous blood samples (5 mL) were drawn under aseptic conditions from ante-cubital vein of study subjects into EDTA vacuum evacuated tubes for glycated hemoglobin estimation using nephrometric method.

Statistical Analysis: Epi Info Statistical software was used to analyze data. Data was entered in Microsoft excel sheet and analyzed using statistical tests such as Chi square test, Analysis of variance, Unpaired Student 't' test, Pearson correlation coefficient was used to determine the correlation between two quantitative variables. p value <0.05 has been considered to be statistically significant.

RESULT:

Table 1: Profile of subjects

		Group A (HbA1c ≥7)		Group B (HbA1c <7)		P value
Age in years	41-50	6	12.0%	12	24.0%	0.058
	51-60	17	34.0%	23	46.0%	
	61-70	22	44.0%	14	28.0%	
	>70	5	10.0%	1	2.0%	
Mean Age (Years)		61.2 ± 8.202		57.0 ± 7.276		0.008*
Sex	Female	24	48.0%	22	44.0%	0.421
	Male	26	52.0%	28	56.0%	
Duration of Diabetes	≤5 years	1	2.0%	36	72.0%	<0.001*
	>5 years	49	98.0%	14	28.0%	
Duration of DM		9.3 ± 3.449		4.5 ± 2.697		<0.01*
FBS		232.5 ± 76.860		109.2 ± 19.253		<0.01*
PPBS		346.5 ± 72.740		163.0 ± 25.988		<0.01*

HbA1C	8.9 ± 0.642	6.2 ± 0.486	<0.01*
Spot Urine Protein Creatinine Ratio	2.4 ± 0.318	0.1 ± 0.043	<0.01*
Serum Creatinine	1.3 ± 0.695	0.9 ± 0.220	<0.01*

In the present study, the majority of subjects in Group A (HbA1c ≥7) were in the age group of 61–70 years (44.0%), while in Group B (HbA1c <7), the majority were in the age group of 51–60 years (46.0%). There was no significant difference in age distribution between the groups (p = 0.058). The mean age in Group A was 61.2 ± 8.202 years, which was significantly higher than Group B, where the mean age was 57.0 ± 7.276 years (p = 0.008). Gender distribution showed no significant difference, with females accounting for 48.0% in Group A and 44.0% in Group B, and males representing 52.0% in Group A and 56.0% in Group B (p = 0.421). The duration of diabetes was significantly longer in Group A (9.3 ± 3.449 years) compared to Group B (4.5 ± 2.697 years, p < 0.01). Mean fasting blood sugar (FBS) levels were significantly higher in Group A (232.5 ± 76.860 mg/dL) compared to Group B (109.2 ± 19.253 mg/dL, p < 0.01). Similarly, postprandial blood sugar (PPBS) levels were significantly elevated in Group A (346.5 ± 72.740 mg/dL) compared to Group B (163.0 ± 25.988 mg/dL, p < 0.01). HbA1c levels were also significantly higher in Group A (8.9 ± 0.642) than Group B (6.2 ± 0.486, p < 0.01). Spot urine protein-creatinine ratio was markedly elevated in Group A (2.4 ± 0.318) compared to Group B (0.1 ± 0.043, p < 0.01). Serum creatinine levels were significantly higher in Group A (1.3 ± 0.695 mg/dL) than in Group B (0.9 ± 0.220 mg/dL, p < 0.01) [Table 1].

Table 2: Urine Albumin comparison between two groups

		Group A		Group B		P value
Urine Albumin	Nil	0	0.0%	31	62.0%	<0.001*
	Trace	0	0.0%	11	22.0%	
	1+	6	12.0%	8	16.0%	
	2+	34	68.0%	0	0.0%	
	3+	10	20.0%	0	0.0%	

In the present study, urine albumin findings showed a significant difference between the two groups (p < 0.001). In Group A, 68.0% of subjects had 2+ albuminuria, followed by 20.0% with 3+ albuminuria, and 12.0% with 1+ albuminuria. In Group B, 62.0% of subjects had no albuminuria, while 22.0% had trace albuminuria, and 16.0% had 1+ albuminuria. Notably, none of the subjects in Group B had 2+ or 3+ albuminuria [Table 2].

Table 3: Fundoscopy findings comparison between two groups

		Group A		Group B		P value
Fundoscopy	No DR	5	10.0%	38	76.0%	<0.001*
	PDR	2	4.0%	0	0.0%	
	Mild NPDR	22	44%	11	22.0%	
	Moderate NPDR	16	32.0%	1	2.0%	
	Severe NPDR	5	10.0%	0	0.0%	

In the present study, fundoscopy findings revealed a significant difference between the two groups (p < 0.001). In Group A, 44.0% of subjects had mild non-proliferative diabetic retinopathy (NPDR), 32.0% had moderate NPDR, 10.0% had severe NPDR, and 4.0% had proliferative diabetic retinopathy (PDR). Only 10.0% of subjects in Group A had no diabetic retinopathy. In contrast, the majority of subjects in Group B (76.0%) had no diabetic retinopathy, while 22.0% had mild NPDR, and 2.0% had moderate NPDR. None of the subjects in Group B had severe NPDR or PDR [Table 3].

Table 4: Correlation of HbA1C with Duration of Diabetes, Spot Urine Protein Creatinine Ratio and Serum Creatinine

		Duration of Diabetes	SUPCR	Serum Creatinine
HbA1C	N	100	100	100
	r value	0.664**	0.961**	0.518**
	p value	<0.01**	<0.01**	<0.01**

In the study there was significant positive correlation between HbA1C and parameters such as Duration of diabetes, SUPCR, Serum creatinine i.e. with increase in HbA1C there was increase in Duration of Diabetes, SUPCR and Serum Creatinine and vice versa [Table 4].

In the present study there is a significant correlation between HbA1C and Spot urine PCR among Group A subjects with a correlation co-efficient of 0.850 [Figure 1].

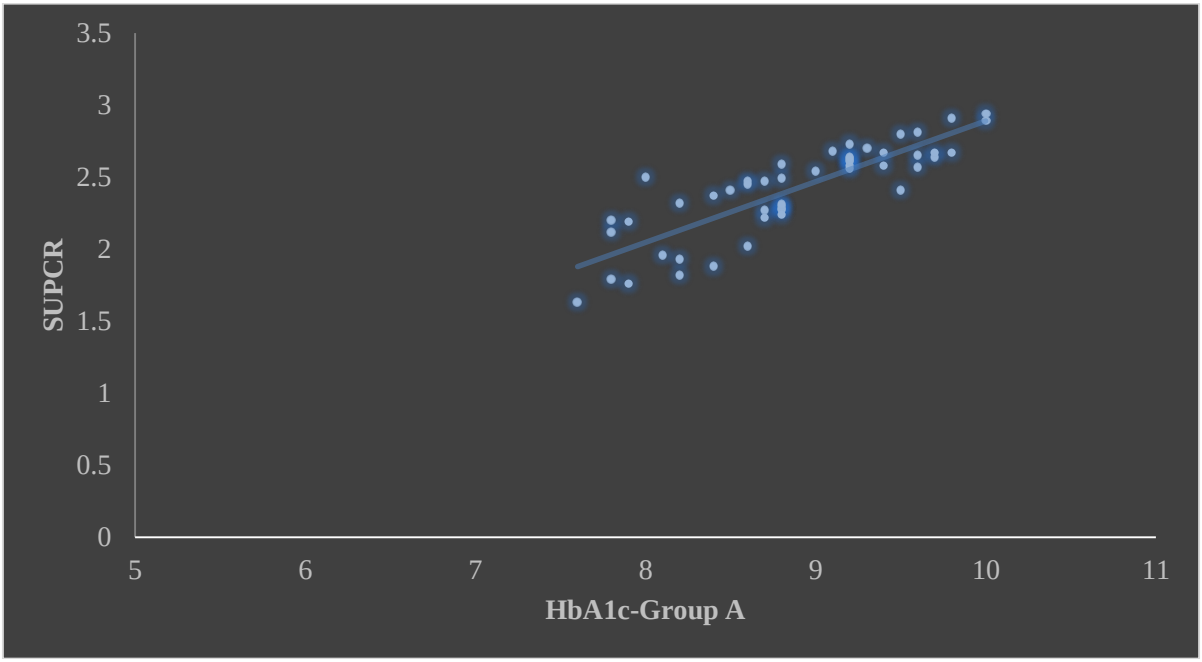

Figure 1: Scatter plot showing Correlation between HbA1c and Spot Urine Protein Creatinine Ratio in Group A

In the present study there is a significant correlation between HbA1C and Spot urine PCR among Group B subjects with a correlation co-efficient of 0.857 [Figure 2].

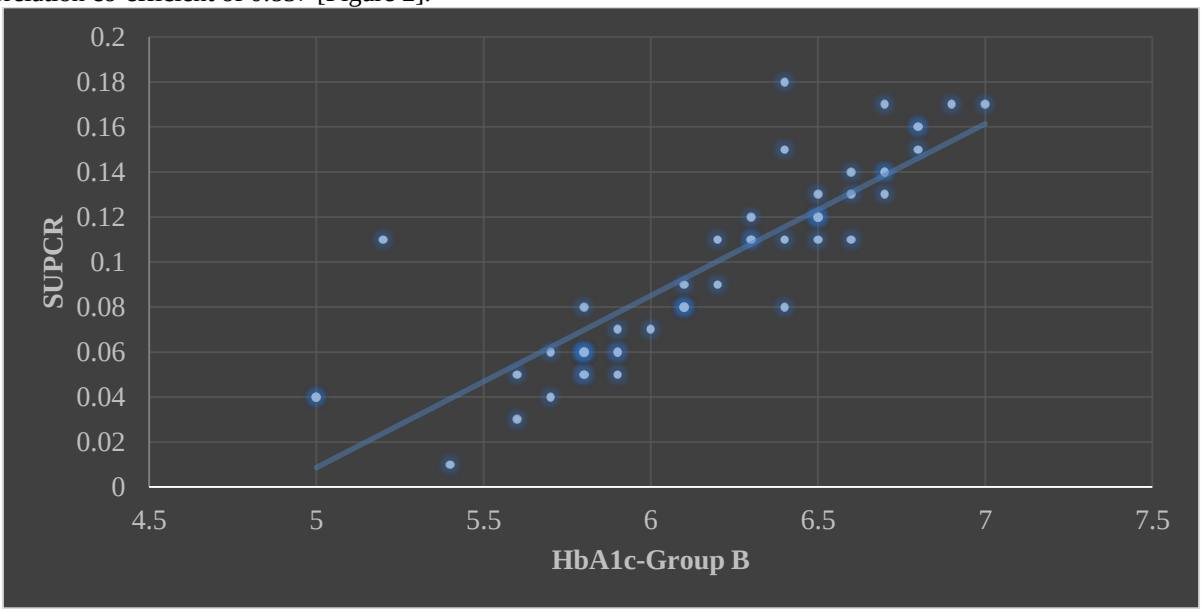

Figure 2: Scatter plot showing Correlation between HbA1c and Spot Urine Protein Creatinine Ratio in Group B

DISCUSSION

In the present study, the age distribution ranged from 40 to 80 years, with the majority of subjects falling within

the 51–70 years age group. The mean age of the subjects was 59.1±8.0, which is comparable to other similar studies, such as Sandip et al.16 (58.8±7.7), Samya et al.17 (58.7±10.5), and Seçmeler et al.18 (60±10.6). A significant association was observed with the studies conducted by Sandip et al.16 and Samya et al.17. The male-to-female ratio in the present study was 1.17:1, which aligns with the findings of Pallavi et al.19 (1.77:1), Vyankatesh et al.20 (1.38:1), and Seçmeler et al.18 (1.32:1). A significant association was noted with the study conducted by Seçmeler et al.18. The mean duration of diabetes since diagnosis in the present study was 9.32±3.5 years, which is comparable to Sandip et al.16 (10.1±3.46 years), Unnikrishnan et al.21 (10.0±6.0 years), and Seçmeler et al.18 (12.23±6.8 years). Significant associations were observed with the studies conducted by Sandip et al.92 and Unnikrishnan et al.21. The mean glycated hemoglobin (HbA1c) in the present study was 7.52±1.48, which was consistent with the findings of Sandip et al.16 (7.68±1.31), Samya et al.17 (7.52±0.8), and Seçmeler et al.18 (7.89±1.4). A significant association was noted with the study conducted by Samya et al.17.

The mean spot urine protein-creatinine ratio (SUPCR) in the present study was 1.26±1.19, which is comparable to the studies conducted by Sunitha et al.22 (1.08±1.28) and Mohammed et al.23 (1.18±1.8). A significant association was observed with the study conducted by Mohammed et al.23. The mean fasting blood sugar in the present study was 170±83.35, which aligns with the findings of Sandip et al.16 (122±21.32) and Sunitha et al.22 (197±89.5). In the present study, the duration of diabetes showed a significant correlation with proteinuria, consistent with the findings of studies conducted by Sandip et al.16 and Seçmeler et al.18. The study also demonstrated a significant correlation between HbA1c and SUPCR, which was comparable to the studies conducted by Sandip et al.92, Samya et al.17, and Seçmeler et al.18. Additionally, the current study revealed a significant correlation between HbA1c, SUPCR, and diabetic retinopathy changes, which was consistent with the findings of Samya et al.17.

CONCLUSION

The study concluded that the spot urine protein-creatinine ratio positively correlates with HbA1c and can serve as an alternative to 24-hour urinary protein estimation, offering a less cumbersome approach. Proteinuria was identified as a major risk factor for the progression of diabetic nephropathy, emphasizing the importance of regular monitoring of HbA1c, blood glucose levels, and early detection and management of proteinuria to prevent disease progression. Additionally, a positive correlation between HbA1c, diabetes duration, and the severity of diabetic retinopathy underscores the necessity of periodic retinopathy screening and HbA1c monitoring to reduce severe late-stage presentations, enhance quality of life, and prevent blindness. Overall, HbA1c and the spot urine protein-creatinine ratio were found to be effective markers for predicting the progression of diabetic nephropathy and retinopathy.

Recommendations and Limitations:

Based on the study findings, regular monitoring of HbA1c and spot urine protein-creatinine ratio (SUPCR) is recommended as effective and practical tools for early detection and monitoring of diabetic nephropathy progression in patients with Type 2 Diabetes Mellitus, particularly in outpatient settings. Emphasis should be placed on achieving optimal glycemic control (HbA1c <7%), routine screening for proteinuria using SUPCR, and periodic fundoscopy for early detection of diabetic retinopathy. These interventions could significantly delay the onset of advanced nephropathy and retinopathy, reduce the associated complications, and improve the quality of life for diabetic patients in rural healthcare settings. Further, targeted education programs and lifestyle interventions focusing on glycemic control and adherence to treatment protocols should be incorporated into patient management plans.

The study is not without limitations. The sample size was relatively small and limited to a single rural tertiary care center, which may limit the generalizability of the findings to broader populations. Furthermore, the cross-sectional nature of the study precludes the establishment of causality between HbA1c, SUPCR, and the progression of diabetic nephropathy and retinopathy. Other confounding factors, such as dietary patterns, physical activity, and genetic predispositions, were not controlled, which might have influenced the results. Future studies with larger sample sizes, multi-center data, and longitudinal follow-ups are essential to validate the findings and explore the long-term impact of glycemic control and SUPCR monitoring on the progression of diabetic complications.

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