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Prevalence and Predictors of Progression of Chronic Kidney Disease in Type 2 Diabetes Mellitus — A Prospective Observational Study

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ABS TRAC T

***Background*:** Diabetic nephropathy is the leading cause of end-stage renal disease worldwide. Early identification of patients at risk for rapid disease progression is critical for timely therapeutic intervention, yet predictive data from Indian tertiary care settings remain scarce. ***Methods*:** This prospective observational study enrolled 180 type 2 diabetes mellitus patients with established CKD stages 2 through 4 (eGFR 15 to 89 mL/min/1.73 m squared) between January and December 2023 at a tertiary nephrology unit in India. Serum creatinine, eGFR (CKD-EPI formula), 24-hour urine protein, HbA1c, lipid profile, and haemoglobin were measured at baseline and every 3 months for 12 months. Rapid progression was defined as an annual eGFR decline exceeding 5 mL/min/1.73 m squared per year. Multivariate Cox regression was used to identify independent predictors. ***Results*:** Mean age was 56.4 plus or minus 10.8 years and 58.9% were male. The median baseline eGFR was 42.6 mL/min/1.73 m squared. Over 12 months the median eGFR decline was 3.8 mL/min/1.73 m squared per year. Rapid progression occurred in 62 patients (34.4%). On multivariate analysis, baseline 24-hour proteinuria above 1 g per day (hazard ratio 3.18, 95% CI 1.84 to 5.50, p less than 0.001), baseline eGFR below 30 (HR 2.74, p equals 0.002), HbA1c above 8% (HR 2.16, p equals 0.012), uncontrolled systolic hypertension above 150 mmHg (HR 1.94, p equals 0.024), and haemoglobin below 10 g/dL (HR 1.82, p equals 0.036) were independent predictors. Use of ACE inhibitors or ARBs was protective (HR 0.54, p equals 0.008). ***Conclusion*:** One in three diabetic CKD patients demonstrated rapid progression over 12 months. Heavy proteinuria and advanced baseline CKD stage were the strongest predictors. Aggressive proteinuria reduction with RAAS blockade, tight glycaemic control, and anaemia correction are recommended to slow progression.

Keywords: *Chronic Kidney Disease, Diabetic Nephropathy, Disease Progression, eGFR Decline, Proteinuria, Type 2 Diabetes.*

INTRODUCTION

Diabetic kidney disease has emerged as the single most common aetiology of chronic kidney disease and end-stage renal disease worldwide, accounting for 30 to 50 percent of incident dialysis patients in most registries [1]. In India, the prevalence of type 2 diabetes mellitus has risen sharply over the past two decades, and with it the burden of diabetic nephropathy has increased proportionally [2]. The natural history of diabetic nephropathy is characterised by an initial phase of glomerular hyperfiltration, followed by progressive albuminuria, declining glomerular filtration rate, and ultimately renal failure requiring dialysis or transplantation [3].

The rate of eGFR decline varies considerably among diabetic patients, and identifying those at risk of rapid progression is of paramount clinical importance. A decline exceeding 5 mL/min/1.73 m squared per year has been widely adopted as the threshold for rapid progression and has been associated with markedly increased risk of reaching end-stage renal disease within 5 to 10 years [4]. Several risk factors for accelerated decline have been identified in Western cohorts, including the magnitude of proteinuria, baseline renal function, glycaemic control, blood pressure, anaemia, and dyslipidaemia [5].

Proteinuria occupies a central position in the pathogenesis and prognostication of diabetic

nephropathy. Beyond its role as a biomarker, filtered protein exerts direct toxic effects on tubular epithelial cells, activating pro-inflammatory and pro-fibrotic pathways that drive tubulointerstitial scarring [6]. The RENAAL and IDNT trials demonstrated that baseline proteinuria was the single strongest predictor of renal outcomes in diabetic nephropathy, surpassing even baseline eGFR [7].

Renin-angiotensin-aldosterone system blockade with ACE inhibitors or angiotensin receptor blockers remains the cornerstone of renoprotective therapy. These agents reduce intraglomerular pressure and proteinuria, and have been shown to slow the rate of eGFR decline by 2 to 3 mL/min per year compared with other antihypertensive agents [8]. However, even with optimal RAAS blockade, a substantial residual risk of progression persists, highlighting the need for additional therapeutic strategies and more precise risk stratification [9].

Data from Indian populations regarding the rate and predictors of CKD progression in diabetic patients are limited. The pattern of risk factors may differ from Western cohorts due to differences in genetic susceptibility, dietary habits, medication access, and healthcare utilisation [10]. The present study was undertaken to evaluate the rate of eGFR decline and identify predictors of rapid CKD progression in type 2 diabetic patients at a tertiary nephrology centre in India.

AIMS AND OBJECTIVES

The present study was undertaken to determine the rate of estimated glomerular filtration rate decline over a 12-month period in type 2 diabetic patients with established chronic kidney disease stages 2 through 4, to ascertain the proportion of patients demonstrating rapid progression defined as an annual eGFR decline exceeding 5 mL/min/1.73 m squared, and to identify independent clinical and laboratory predictors of rapid progression using multivariate regression analysis.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational cohort study was conducted from January to December 2023 at the Department of Nephrology, Government Tertiary Care Teaching Hospital, India. The study was approved by the Institutional Ethics Committee and all patients provided written informed consent.

Sample Size

A total of 180 patients were enrolled. The sample size was estimated using the formula for detecting a 30% event rate (rapid progression) with 95% confidence interval and 7% absolute precision, yielding a minimum of 165 subjects, rounded to 180 to account for potential attrition.

Inclusion Criteria

Adults aged 18 years and above with established type 2 diabetes mellitus of at least 2 years duration and CKD stages 2 through 4 defined as eGFR between 15 and 89 mL/min/1.73 m squared (CKD-EPI equation) on at least two measurements taken 3 months apart, who were willing to attend quarterly follow-up visits for 12 months, were included.

Exclusion Criteria

Patients with type 1 diabetes, non-diabetic kidney disease confirmed by biopsy or clinical features, rapidly progressive glomerulonephritis, obstructive uropathy, active malignancy, pregnancy, organ transplant recipients, patients already on dialysis, and those unable to provide informed consent were excluded.

Procedure and Data Collection

At enrolment, a detailed history was obtained including diabetes duration, antidiabetic and antihypertensive medications, smoking status, and family history. Physical examination included blood pressure measurement (mean of two seated readings after 5 minutes rest), BMI, and assessment for peripheral oedema and diabetic retinopathy status. Laboratory investigations performed at baseline and at 3, 6, 9, and 12 months included serum creatinine (Jaffe kinetic method, IDMS-traceable), blood urea nitrogen, serum electrolytes, fasting plasma glucose, HbA1c (HPLC method), lipid profile, complete blood count with haemoglobin, serum albumin, calcium, phosphorus, and intact PTH. Twenty-four-hour urine collections were obtained at baseline, 6, and 12 months for quantification of proteinuria and creatinine clearance. Spot urine albumin-to-creatinine ratio was also measured at each visit. eGFR was calculated using the CKD-EPI equation. Renal ultrasonography was performed at baseline. The rate of eGFR decline was computed by linear regression of all available eGFR measurements over the 12-month period for each patient.

Follow-Up Protocol

Patients were seen at 3-month intervals for a total of 5 visits (baseline plus 4 follow-ups). At each visit, clinical assessment, medication review, and blood sampling were performed. Treatment modifications including adjustment of antihypertensive therapy, RAAS blockade optimisation, and glycaemic management were made by the treating physician according to standard guidelines. Patients who progressed to ESRD requiring dialysis initiation during the study period were documented and included in the analysis.

Statistical Analysis

Data were entered in Microsoft Excel and analysed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean plus or minus standard deviation or median with interquartile range as appropriate and compared using

the Student t-test or Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test. The primary outcome (rapid progression) was analysed using multivariate Cox proportional hazards regression with backward stepwise elimination. Variables with p less than 0.10 on univariate analysis were entered into the multivariate model. Kaplan-Meier analysis with log-rank test was used to compare time to composite renal endpoint (50% eGFR decline, ESRD, or death) between groups. A two-tailed p-value less than 0.05 was considered statistically significant.

RESULTS

Of 180 enrolled patients, 172 completed the 12-month follow-up (attrition 4.4%). Eight patients were lost to follow-up: 3 relocated, 3 died from cardiovascular causes, and 2 withdrew consent. The baseline characteristics are presented in Table 1. The mean age was 56.4 plus or minus 10.8 years, 58.9% were male, and the mean diabetes duration was 12.4 plus or minus 6.2 years. The median baseline eGFR was 42.6 mL/min/1.73 m squared (IQR 28.4 to 58.2). CKD stage distribution was Stage 2 in 32 patients (17.8%), Stage 3a in 48 (26.7%), Stage 3b in 56 (31.1%), and Stage 4 in 44 (24.4%). Mean baseline HbA1c was 8.2 plus or minus 1.6%, mean 24-hour proteinuria was 1.4 plus or minus 1.2 g per day, and mean haemoglobin was 11.2 plus or minus 1.8 g/dL. ACE inhibitor or ARB use at baseline was documented in 124 patients (68.9%).

The overall median rate of eGFR decline was 3.8 mL/min/1.73 m squared per year (IQR 1.6 to 6.4). Rapid progression (eGFR decline exceeding 5 mL/min per year) occurred in 62 patients (34.4%). During the study period, 12 patients (6.7%) reached ESRD requiring dialysis initiation and 3 patients (1.7%) died from cardiovascular events.

The comparison between rapid and non-rapid progressors is presented in Table 2. Rapid progressors had significantly higher baseline proteinuria (2.4 plus or minus 1.4 versus 0.9 plus or minus 0.6 g/day, p less than 0.001), lower baseline eGFR (34.2 plus or minus 12.8 versus 48.4 plus or minus 16.2, p less than 0.001), higher HbA1c (8.8 plus or minus 1.8 versus 7.8 plus or minus 1.4%, p less than 0.001), higher systolic BP (148.6 plus or minus 18.4 versus 136.2 plus or minus 14.8 mmHg, p less than 0.001), and lower haemoglobin (10.2 plus or minus 1.6 versus 11.8 plus or minus 1.6 g/dL, p less than 0.001).

Multivariate Cox regression results are presented in Table 3. Baseline proteinuria above 1 g/day (HR 3.18, 95% CI 1.84 to 5.50, p less than 0.001), eGFR below 30 (HR 2.74, 95% CI 1.56 to 4.82, p equals 0.002), HbA1c above 8% (HR 2.16, 95% CI 1.28 to 3.64, p equals 0.012), uncontrolled SBP above 150 (HR 1.94, 95% CI 1.14 to 3.30, p equals 0.024), and haemoglobin below 10 (HR 1.82, 95% CI 1.04 to 3.18, p equals 0.036) independently predicted rapid progression. ACE inhibitor or ARB use was protective (HR 0.54, 95% CI 0.34 to 0.86, p equals 0.008).

Kaplan-Meier analysis demonstrated that patients with proteinuria above 1 g/day had significantly worse renal survival compared to those with proteinuria below 1 g/day (log-rank p less than 0.001). The 12-month composite renal endpoint (50% eGFR decline or ESRD) occurred in 28 patients (15.6%), with significantly higher rates in CKD Stage 4 (29.5%) compared to Stage 3b (14.3%), Stage 3a (8.3%), and Stage 2 (3.1%, p less than 0.001).

Table 1: Baseline Demographic and Clinical Characteristics (n = 180)

Parameter	Value
Age (years), Mean +/- SD	56.4 +/- 10.8
Male, n (%)	106 (58.9%)
DM duration (years)	12.4 +/- 6.2
BMI (kg/m2)	26.2 +/- 4.4
SBP (mmHg)	140.6 +/- 16.8
DBP (mmHg)	84.2 +/- 10.4
eGFR (mL/min), Median (IQR)	42.6 (28.4-58.2)
24h proteinuria (g/day)	1.4 +/- 1.2
HbA1c (%)	8.2 +/- 1.6
Haemoglobin (g/dL)	11.2 +/- 1.8
ACEi/ARB use, n (%)	124 (68.9%)
Diabetic retinopathy, n (%)	98 (54.4%)
Current smoker, n (%)	32 (17.8%)

Table 2: Comparison — Rapid vs Non-Rapid Progressors

Parameter	Rapid (n=62)	Non-rapid (n=118)	p-value
Age (years)	58.2 +/- 10.4	55.4 +/- 10.8	0.094
Baseline eGFR	34.2 +/- 12.8	48.4 +/- 16.2	<0.001
24h proteinuria (g/day)	2.4 +/- 1.4	0.9 +/- 0.6	<0.001

HbA1c (%)	8.8 +/- 1.8	7.8 +/- 1.4	<0.001
SBP (mmHg)	148.6 +/- 18.4	136.2 +/- 14.8	<0.001
Hb (g/dL)	10.2 +/- 1.6	11.8 +/- 1.6	<0.001
ACEi/ARB use (%)	54.8%	76.3%	0.004
Retinopathy (%)	72.6%	44.9%	<0.001

Table 3: Predictors of Rapid Progression — Multivariate Cox Regression

Predictor	HR	95% CI	p-value
Proteinuria > 1 g/day	3.18	1.84 - 5.50	<0.001
eGFR < 30 mL/min	2.74	1.56 - 4.82	0.002
HbA1c > 8%	2.16	1.28 - 3.64	0.012
SBP > 150 mmHg	1.94	1.14 - 3.30	0.024
Hb < 10 g/dL	1.82	1.04 - 3.18	0.036
ACEi/ARB use	0.54	0.34 - 0.86	0.008
Smoking	1.48	0.86 - 2.54	0.158
LDL > 130 mg/dL	1.36	0.82 - 2.26	0.234

Table 4: Rate of eGFR Decline by CKD Stage

CKD Stage	n	Baseline eGFR	Annual eGFR Decline	Rapid Progressors (%)
Stage 2	32	72.4 +/- 8.6	2.4 +/- 1.8	15.6%
Stage 3a	48	52.6 +/- 6.4	3.2 +/- 2.4	25.0%
Stage 3b	56	38.2 +/- 5.8	4.2 +/- 3.2	37.5%
Stage 4	44	22.8 +/- 4.6	5.8 +/- 3.6	52.3%

Table 5: Composite Renal Endpoint at 12 Months by Subgroup

Subgroup	Event Rate	p-value
Proteinuria > 1 g/day	26.4%	<0.001 vs < 1 g/day
Proteinuria < 1 g/day	6.8%	Reference
HbA1c > 8%	22.6%	0.004 vs <= 8%
HbA1c <= 8%	9.2%	Reference
On ACEi/ARB	11.3%	0.012 vs not on ACEi/ARB
Not on ACEi/ARB	24.6%	Reference

Table 6: Changes in Key Parameters Over 12 Months

Parameter	Baseline	6 Months	12 Months	p-value
eGFR (mL/min)	42.6	40.2	38.4	<0.001
Proteinuria (g/day)	1.4	1.2	1.1	0.042
HbA1c (%)	8.2	7.8	7.6	<0.001
SBP (mmHg)	140.6	136.4	134.8	0.002
Hb (g/dL)	11.2	11.0	10.8	0.086

DISCUSSION

The finding that 34.4% of patients demonstrated rapid eGFR decline is consistent with the 30 to 40% range reported by Keane *et al*., [11] in the RENAAL trial population. The median annual eGFR decline of 3.8 mL/min per year is comparable to the 3.5 to 4.0 mL/min per year reported by Babazono *et al*., [12] in Japanese diabetic patients and the 4.2 mL/min per year reported by Rossing *et al.*, [13] in Danish patients with overt diabetic nephropathy.

Baseline proteinuria emerged as the strongest predictor of rapid progression (HR 3.18), reinforcing the findings of de Zeeuw *et al*., [14] who demonstrated that baseline albuminuria was the single most powerful predictor of renal outcome in the RENAAL and IDNT trials. The magnitude of this association underscores the importance of proteinuria reduction as a therapeutic target in diabetic nephropathy.

The protective effect of ACE inhibitor or ARB use (HR 0.54) is consistent with the landmark trials establishing the renoprotective efficacy of RAAS blockade. However, the finding that 31.1% of patients were not receiving RAAS blockade at baseline highlights a significant treatment gap. Ruggenenti *et al*., [15] demonstrated that maximisation of RAAS blockade reduced proteinuria by an additional 30 to 40% in patients already on standard doses.

The association between poor glycaemic control (HbA1c above 8%) and rapid progression (HR 2.16) supports the findings of the UKPDS [16], which showed that each 1% reduction in HbA1c was associated with a 37% decrease in microvascular complications. However, the ACCORD trial cautioned

that excessively tight glycaemic control in patients with advanced CKD may increase mortality risk [17].

Anaemia as an independent predictor (HR 1.82) is consistent with the observations of Mohanram *et al*., [18] who reported that each 1 g/dL decrease in haemoglobin was associated with a 11% increase in the risk of renal outcomes. Anaemia in diabetic CKD results from erythropoietin deficiency, iron deficiency, and chronic inflammation, and may contribute to renal progression through tissue hypoxia and oxidative stress.

The study had certain limitations. The relatively short 12-month follow-up may underestimate long-term progression rates. The use of the Jaffe method for creatinine measurement, while IDMS-traceable, may introduce minor analytical variation. Tubular biomarkers such as NGAL and KIM-1 were not measured, which might have provided additional prognostic information [19]. Finally, dietary protein and sodium intake, which influence proteinuria and progression, were not systematically assessed [20].

CONCLUSION

One in three type 2 diabetic patients with established CKD demonstrated rapid eGFR progression over 12 months. Proteinuria exceeding 1 gram per day was the strongest independent predictor, followed by advanced CKD stage, poor glycaemic control, uncontrolled hypertension, and anaemia. RAAS blockade with ACE inhibitors or ARBs conferred significant renoprotection. A treatment gap was identified, with nearly one-third of eligible patients not receiving RAAS blockade. These findings support an aggressive, multifactorial approach incorporating maximal tolerated RAAS blockade, glycaemic optimisation to an HbA1c target of 7 to 8%, blood pressure control below 130/80 mmHg, and correction of anaemia to slow the progression of diabetic kidney disease.

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