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Study of clinical and histopathological factors predicting rapid progression in biopsy-proven type 2 diabetic kidney disease

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ABSTRACT

Introduction: Rapid progression of diabetic kidney disease (DKD) is a significant concern, particularly in developing countries. It remains uncertain whether histopathological parameters, in addition to clinical factors, can predict DKD progression.

Objectives: To evaluate renal histopathological and clinical parameters in predicting rapid progression to end-stage kidney disease (ESKD) in type 2 diabetes mellitus (Type 2 DM) patients with biopsy-proven DKD.

Patients and Methods: This was an observational retrospective study that included 49 biopsy-proven DKD from January 2018 to December 2022. Those with less than six months of follow-up and CKD stage 5 were excluded. The outcomes studied were rapid progression and progression to ESKD. Patients were categorized into rapid progressors and non-progressors based on the estimated glomerular filtration (eGFR) decline of > or <10 mL/min/1.73 m^2/year, respectively. The association of histopathological factors and clinical parameters with rapid progression and independent risk factors for progression to ESKD were analysed using SPSS 22.

Results: In a median follow-up of 1.6 years, 57% were rapid progressors, and 42.9% were non-progressors, with a median eGFR decline of 21 mL/min/1.73 m^2/year and 5 mL/min/1.73 m^2/year, respectively. Among histopathological factors, global glomerular sclerosis (class 4) predicted rapid progression ($P=0.03$), since among clinical factors, hypertension (89.3%) elevated hemoglobin A1c (HbA1c) (9.6%), and massive proteinuria (75.1%) were significant parameters associated with rapid progression ($P<0.05$). In Cox regression analysis, the progression to ESKD was independently associated with global glomerular sclerosis (HR 1.1, CI 1.0-1.4, $P=0.04$) and massive proteinuria (HR 1.6, CI 1.0-2.1, $P=0.01$)

Conclusion: In our cohort, hypertension, high HbA1c, severe proteinuria, and global glomerular sclerosis (Class 4) were associated with rapid progression. Severe proteinuria and global glomerular sclerosis were independent risk factors for progression to ESKD. This highlights the need for large prospective studies in identifying the factors predicting rapid progressors in DKD; therefore, timely intervention can be considered.

Original Article

Implication for health policy/practice/research/medical education:
In DKD, renal function can rapidly worsen to ESKD. To develop methods for preventing or delaying disease progression and reducing complications, which would improve quality of life and disease outcomes, it is important to identify potential risk factors that might be affecting the rapid progression of DKD. It remains uncertain whether histopathological parameters and clinical factors can predict DKD progression.

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Introduction

Diabetic kidney disease (DKD) emerges as a prevalent long-term complication that occurs in 20%-40% of patients diagnosed with type 2 diabetes mellitus (type 2 DM) (1). Renal function in individuals with DKD typically declines gradually. However, a significant number of patients experience rapid progression, leading to end-stage kidney disease (ESKD) that requires renal replacement therapies (2,3).

Due to the heterogeneity of estimated glomerular filtration (eGFR) decline with the risk of progression, the global challenge of identifying rapid progressors persists (4). Various risk factors, including clinical and biochemical histopathological indicators, can predict the rapid progression of DKD. Among these factors, proteinuria is considered a widely proven standard indicator.

Although kidney biopsy is rarely conducted to diagnose DKD, it can provide substantial structural insights that can potentially contribute to the loss of renal function (5). Some longitudinal studies have demonstrated the association between the severity of pathological changes and renal prognosis (6,7). Still, few studies have provided the specific histological characteristics that predict renal prognosis (8). However, the results of previous studies were conflicting, and thus, the predictive value of histopathological risk factors contributing to rapid progression remains inconclusive. Moreover, there is a sparsity of data in developing countries. Thus, to better understand the course of rapid progression, we conducted a retrospective cohort study in type 2 diabetes patients with biopsy-proven DKD to assess the association of histological factors in addition to clinical characteristics, to predict the rapid progression to ESKD in DKD.

Objectives

To evaluate renal histopathological and clinical parameters in predicting rapid progression to ESKD in type 2 DM patients with biopsy-proven DKD.

Patients and Methods

Study population

We conducted a retrospective observational cohort study at Kasturba Medical College including T2DM who had undergone native kidney biopsy from January 2018 to January 2022 and were histologically proven DKD with a minimum of six months follow-up. Those with less than six months follow-up, chronic kidney disease (CKD) 5, and those without clinical information were excluded from the study.

Data collection

Data at the time of biopsy were taken as baseline findings, and from the date of biopsy until the patient had either reached ESKD or lost to follow-up were considered as post-biopsy follow-up data. Clinical details including age, gender, body mass index (BMI), duration of diabetes and hypertension, dyslipidemia, and laboratory data including serum creatinine, eGFR based on chronic kidney disease epidemiology collaboration (CKD-EPI) equation, 24-hour urine protein, and hemoglobin A1c (HbA1c) were collected as baseline data from electronic medical records. Histological findings, including glomerular lesions, tubular interstitial, and vessel involvement, were studied. Four classes of glomerular lesions, including class I (mild and non-specific light microscopic changes), class II (mesangial expansion), class III (nodular sclerosis), and class IV (advanced diabetic glomerulosclerosis) (5), were analysed. Similarly, interstitial fibrosis and tubular atrophy (IFTA) scores (0- 3), interstitial inflammation (0-2), arteriolar sclerosis (1-2), and arteriolar hyalinosis were also quantified. A single dedicated nephropathologist evaluated biopsies.

Based on the post-biopsy eGFR decline, patients were grouped into rapid progressors and non-progressors at the end of the follow-up. The primary outcomes studied were the risk factors for rapid progression and progression to ESKD.

Definitions

eGFR and CKD staging: "CKD-EPI equation was used to estimate eGFR using the serum creatinine, GFR = 141 × min (Scr/ κ, 1) α × max (Scr/ κ,1)-1.209 × 0.993Age (×1.018(if female) (×1.159 if black), where Scr addressed the serum creatinine in mg/dl, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and - 0.411 for males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1". The patients were categorized into CKD stages as per KDIGO criteria (9, 10).

Proteinuria: Proteinuria was classified into mild (0.5-1 g/24 h), moderate (1-3 g/24 h), and severe (>3.5 g/24 h).

Rapid progressors: Sustained decline of >10 mL/min per 1.73 m^2/year in eGFR (11).

Non-progressors: Decline in eGFR <10 mL/min per 1.73 m^2/year

ESKD: ESKD was defined as the eGFR decline to <15ml/min/1.73 m^2 or the need for renal replacement therapy (12).

Statistical analysis

The normal distribution of data was tested by the Shapiro test. Mean ± SD represents continuous variables, whereas median with interquartile range is used for non-continuous variables. Percentages of categorical variables were compared using chi-square or Fisher exact test. We

used t-tests and the Mann-Whitney U test to compare the mean and median for continuous variables. Spearman's correlation analysis was conducted to find the correlation between the eGFR decline, and histological and clinical characteristics. Independent risk factors for progression to ESKD were identified using Cox regression analysis. We analyzed renal survival rates using Kaplan-Meier analysis and compared survival rates for histological parameters with the log-rank (Mantel-Cox) test, for which histological scores and proteinuria classes were reclassified into dichotomous variables. A *P* value of ≤0.05 was considered as statistically significant result.

Results

A total of 118 T2DM patients who had undergone renal biopsy were screened for the study, and 49 biopsy-proven DKD patients were included in the study as shown in Figure 1. Patients were followed up for a median period of 1.6 years (IQR 1.3, 2.2).

Clinical characteristics

Based on the post-biopsy annual eGFR decline, 28/49 (57%) patients had rapid progression, and 21/49 (43%) were non-rapid progressors. The baseline clinical characteristics are summarized in Table 1. Rapid progressors had a significantly higher incidence of hypertension (89.3% versus 65.8%, $P=0.001$), along with severe proteinuria (75.1 versus 28.5, $P=0.001$, Figure 2), with the median 24-hour proteinuria being 5.5 g/d (IQR 3.9, 7. 2), and further elevated HbA1c (9.6 versus 6.5, $P=0.05$) compared to non-progressors. The median serum creatinine and eGFR decline within groups were 2.09 mg/dL versus 1.5 mg/dL and 21 mL/min/1.73 m^2/year versus 5.5 mL/min/1.73 m^2/year, respectively ($P=0.01$). No statistical difference was observed in terms of age, BMI, dyslipidemia, duration of diabetes and hypertension, and microvascular complications such as diabetic retinopathy, diabetic neuropathy, and cardiovascular disease ($P>0.05$). A total of 17.8% were observed with CVD, and the majority of patients (18.4%) had ischemic heart disease. In the CKD grouping, the majority of rapid progressors were at baseline CKD group 3.

Pathological features

We compared the histological characteristics among the progressors and non-progressors groups, as shown in Table 2. We combined glomerular class 11a and 11b for analysis. Arteriolar hyalinosis was not compared because all had a score of 2. Among the histological parameters, glomerular lesions differed significantly between groups ($P=0.03$), where the majority of rapid progressors were observed with global glomerulosclerosis (57.1%, $P=0.03$). In comparison, IFTA (0.2), interstitial inflammation (0.2), and arteriosclerosis (0.3) did not exhibit statistical significance ($P>0.05$).

Spearman's rank correlation coefficients were calculated between clinical variables and histological parameters with GFR decline (Figure 3), where only proteinuria showed

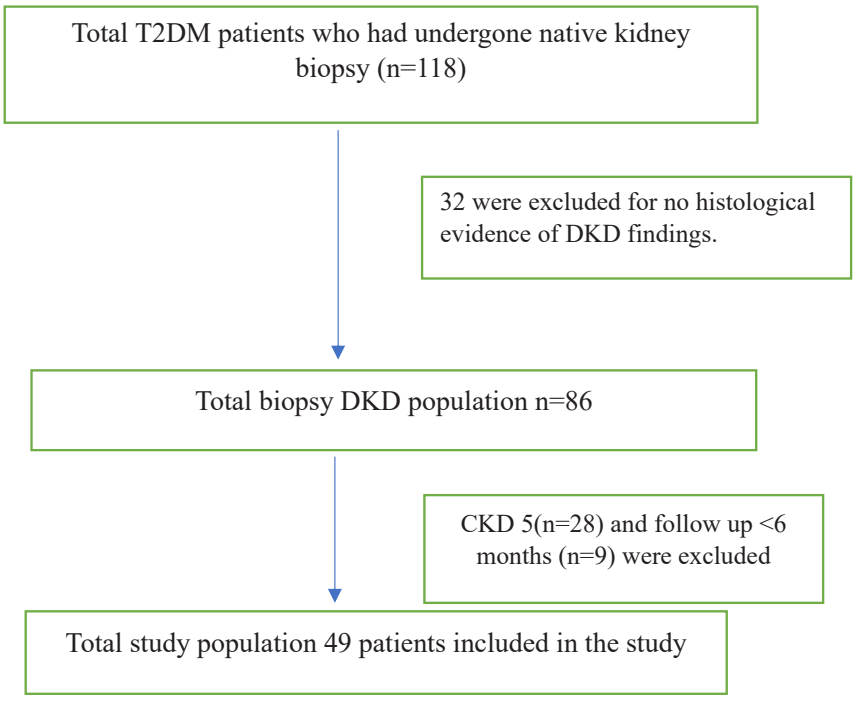

Figure 1. Consort diagram.

Table 1. Baseline clinical characteristics

Characteristics	Overall (n=49)	Rapid progressors (n=28)	Non-progressors (n=21)	*P* value
Age (years)	67.8±8.2	69.2±8.3	64.2±9.3	0.08
Males, n (%)	41 (83.7)	24 (85.7)	17 (81.7)	0.06
BMI (kg/m^2)	25.0 (23.4-29.6)	27.9 (24.6-29.6)	25 (23.3-29.0)	0.5
Hypertension, n (%)	46 (93.9)	32 (89.3)	14 (65.8)	0.01
Duration of diabetes (y)	10 (7-16)	10 (8-16)	10 (6.5-15.5)	0.7
Duration of hypertension (y)	7 (4-14)	7 (3-17)	7 (4-11)	0.7
Dyslipidemia, n (%)	9 (18.6)	4 (16.2)	5 (20.8)	0.58
HbA1c (%)	7.6 (6.8-9.9)	9.6 (6.9-10.4)	6.5 (6.8-7.3)	0.04
Serum creatinine (mg/dL)	1.9 (1.3-2.5)	2.09 (1.5-2.8)	1.5 (1.2-2.1)	0.08
eGFR (mL/min/1.73 m^2/year)	39 (27-61)	48.5 (31-67.5)	38 (23.5-48)	0.13
eGFR decline (mL/min/1.73 m^2/year)	10.5 (27.0-5.8)	21 (38.7- 14.25)	5.5 (6.8-2.2)	0.001
ESKD	21 (42.8)	17 (60.2)	5 (23.0)	0.01
24-hours protein (g/24 h)	3.7 (2.5-5.9)	5.5 (3.9-7.2)	2.4 (1.5-3.3)	0.001
Mild (0.5-1 g/24 h)	12 (24.4)	3 (10.7)	9 (42.0)	0.03
Moderate (1-3 g/24 h)	10 (20.4)	4 (14.2)	6 (28.3)	0.06
Massive (>3 g/24 h)	27 (55.1)	21 (75.1)	6 (28.5)	0.001
Microvascular complications				
Diabetic retinopathy, n (%)	25 (51.0)	15 (53.6)	10 (47.6)	0.509
Diabetic neuropathy, n (%)	6 (12.2)	3 (10.7)	3 (14.2)	0.476
CVD, n (%)	9 (18.3)	5 (17.8)	4 (19.0)	0.48
PVD, n (%)	9 (18.3)	5 (17.8)	4 (19.0)	0.226
CKD stages, n (%)				
G1	7 (14.2)	2 (7.14)	5 (23.8)	0.53
G2	5 (10.2)	2 (7.14)	3 (14.2)	0.38
G3	28 (57.1)	18 (64.2)	10 (47.6)	0.04
G4	9 (18.3)	6 (21.3)	3 (14.2)	0.18

BMI, Body mass index; CVD, Cardiovascular disease; PVD, Peripheral vascular disease; CKD, Chronic kidney disease; eGFR, estimated glomerular filtration rate.

a strong correlation (rho-0.53, $P=0.001$) and weak correlation with glomerular classes (rho-0.29, $P=0.03$).

Clinical and pathological risk factors associated with progression to ESKD

Among progressors, 60% (n=17) progressed to ESKD. In Kaplan-Meier analysis, a significant difference in renal survival was observed between glomerular classes 3 and 4 (log-rank $P=0.008$), as well as between severe and minimal proteinuria (log-rank $P=0.02$) (Figure 4). Consistent with this, Cox proportional hazard analysis severe proteinuria (HR1.6, CI: 1.0-2.1, $P=0.001$) and global glomerular sclerosis (HR 1.1, CI: 1.0-1.4, $P=0.04$) were the potential risk factors associated with progression to ESKD.

Discussion

A significant proportion of patients with DKD undergo rapid progression, which was first identified in 1990 among Pima Indians with a mean eGFR loss of 16 mL/min/1.73 m^2/year (13), later it has been reported in other ethnicities as well (14). In this study, we have chosen a cut-off of >10 mL/min/1.73 m^2 annual decline, which showed 57% of biopsy-proven DKD patients were rapid progressors with a median annual GFR slope of 21 mL/min/1.73 m^2. With a similar cut-off, the study by Krolewski et al observed that 21% of type 2 diabetes had rapid progression (15). Additionally, a South Asian cross-sectional study reported that 30% of the study population had rapid progression to ESKD within a

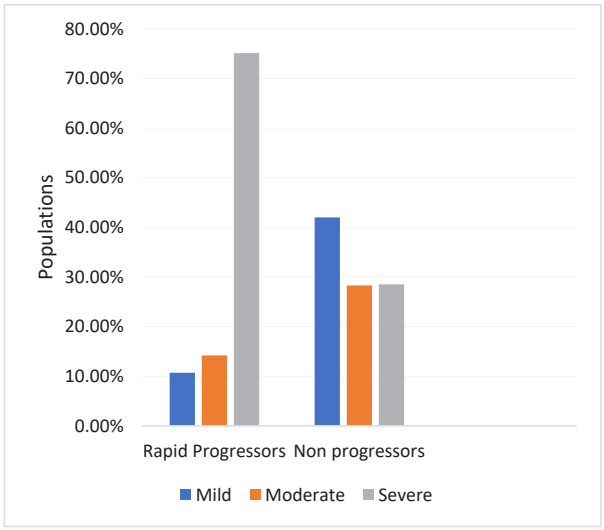

Figure 2. Trends of proteinuria.

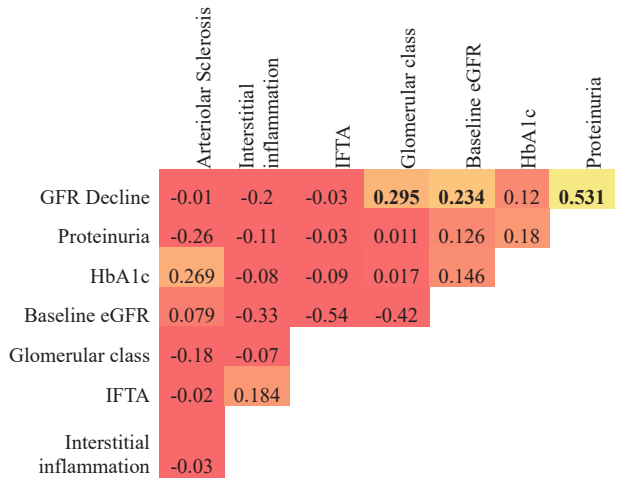

Figure 3. Correlation between GFR decline, histology scores, and clinical parameters.

mean eGFR loss of 17.5±19.3 mL min/1.73 m^2 (14). Two studies within the Chinese population have documented rapid progression, wherein in the study by Qin et al (2), 54.2% had rapid GFR decliners, similarly, Wang et al (16) found 70% of their population were rapid progressors, both demonstrating a median annual GFR fall of -8 mL/min/1.73 m^2 using a simple linear model for eGFR loss over time(15). The variability in the incidence of rapid progression observed across studies can be attributed to the use of diverse criteria for defining annual GFR decline and differences in race and demography.

Identifying the patients with a high risk for rapid progression can facilitate timely and appropriate interventions to delay the disease progression to ESKD (14). By analyzing the clinical characteristics, we observed the majority of the rapid progressors were elderly, which was similar to Zoppini et al (4) and Misra et al (11). Inconsistent with these, the mean age of South Asian individuals exhibiting rapid progression was reported to be younger age (mean age 49±12.7 years), where the onset of type 2 diabetes majority was at a younger age in their study cohort. Our study group observed a significant association between rapid progression and poor glycaemic control, characterized by a median HbA1c of 9.6% (6.9,10.4), which was consistent with Misra et al where they reported a median of 9.0% (6.8,11.8) (11).

Table 2. Baseline pathological features

Characteristics	Overall (n=49)	Rapid progressors (n=28, 57.1%)	Non-progressors (n=21, 42.9%)	*P* value
Glomerular class, n (%)				0.03
Class 2	4	-	4 (19.0)	
Class 3	22 (44.8)	12 (42.8)	10 (47.6)	
Class 4	23 (46.9)	16 (57.1)	7 (33.3)	
Interstitial fibrosis and tubular atrophy score, n (%)				0.245
0	5 (10.2)	4 (14.3)	1 (4.8)	
1	16 (32.6)	8 (28.5)	8 (38.6)	
2	10 (20.4)	5 (17.8)	5 (23.8)	
3	18 (36.7)	11 (39.2)	7 (33.5)	
Interstitial inflammation, n (%)				0.258
0	4 (8.2)	3 (10.7)	1 (4.8)	
1	41 (83.7)	24 (85.7)	17 (81.0)	
2	4 (8.2)	1 (3.6)	3 (14.3)	
Arteriolar sclerosis, n (%)				0.34
1	45 (91.8)	26 (92.9)	19 (90.5)	
2	4 (8.2)	2 (7.2)	2 (9.5)	

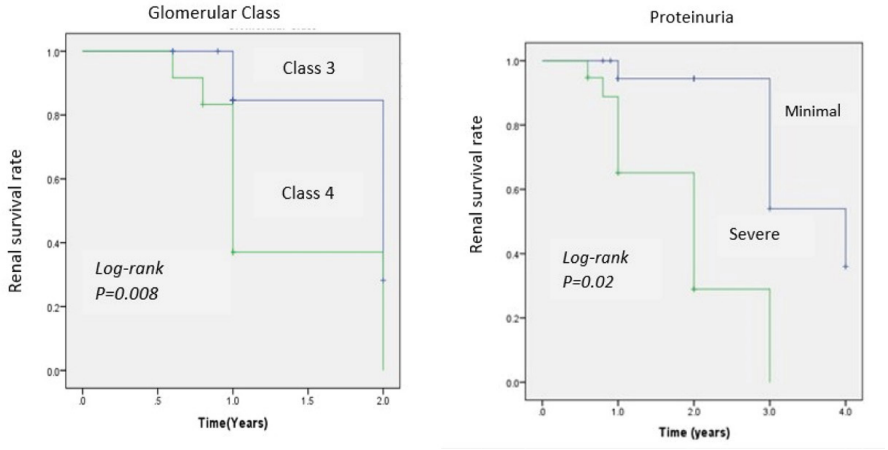

Figure 4. Renal survival analysis curve.

The association between HbA1c and rapid GFR decline was further highlighted in both the Joslin kidney study (15) and the Japan Diabetes complication study cohort (17). Advance trial reported the progression to ESKD was reduced to 65% among the good glycaemic control group (18). Further, we observed a significant association between rapid progression and hypertension, which was seen in 89.3% of the population as a comorbid disease. These findings align with another South Asian study in which 82.6% of rapid progressors were found to have coexisting hypertension (14). In line with these, Japanese and Caucasian population studies also observed a high prevalence of rapid decliners among the hypertensive group (4,17). These suggest that effective glycaemic and blood pressure control can potentially mitigate further progression of DKD.

Severe proteinuria was strongly associated with rapid annual GFR decline and a strong predictor for subsequent progression to ESKD, with median proteinuria of 5.5 g/24 h. This was similar to many other studies (18-20). Likewise, Wang et al reported the mean GFR decline was 20.65 ml/min/1.73 m^2 within the severe proteinuria group which was higher compared to the moderate proteinuria group (16). Further, in the Joslin kidney study, 17% to 21% of rapid decliners were found in those with proteinuria (15). Thus, the nephrotic range of proteinuria is an established risk factor for the disease progression (16,21).

Histologically, global glomerular sclerosis was predominant in rapid progressors, a pattern that resonated with findings from another South Asian study conducted by Yaqub et al (14) as well as a case report documented by Lim et al (19).While a retrospective study involving 377 Japanese patients with biopsy-proven DKD found that nodular sclerosis was significantly linked to an annual eGFR decline of ≥5 mL/min/1.73m^2 (20). In risk factor analysis, only advanced glomerular lesions were independently associated with the risk of rapid progression to ESKD. However, contradicting this finding, Misra et al demonstrated that the IFTA score was an independent risk factor for ESKD. Okada et al reported that only interstitial lesions but not glomerular lesions were independent predictors of renal outcomes (21). Whereas, Yu et al study identified both glomerular and interstitial lesions as predictors of ESKD. In our study, we also noted a significant difference in renal survival rates between glomerular class 4 and other classes (1, 2 and 3), which was consistent with Yu et al (22). Histological scores including IFTA, arteriosclerosis, and arteriolar hyalinosis were not a strong predictor of rapid progression, which was consistent with Misra et al and Okada et al findings (11,21) suggesting the pathological risk factors vary among study populations. This variation can be attributed to several factors, including diversity in ethnicity and differences in healthcare practices across the population studies.

Conclusion

We found clinical parameters, including the coexistence of hypertension, HbA1c, severe proteinuria, and histologically glomerular lesions were more prevalent in rapid GFR decliners. Furthermore, severe proteinuria and glomerular classes were independently associated with rapid progression to ESKD. To validate these findings, conducting longer follow-up multicentre studies with more diverse patient populations is essential.

Limitations of the study

The study was a retrospective single centred with a small cohort.

Authors' contribution

Conceptualization: Shankar Prasad Nagaraju, Shilna Muttickal Swaminathan, and Mohan V Bhojaraja.

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Funding acquisition: Shankar Prasad Nagaraju, Ravindra Prabhu Attur, and Mohan V Bhojaraja.

Investigation: Shankar Prasad Nagaraju, Shilna Muttickal Swaminathan, Mohan V Bhojaraja and Ravindra Prabhu Attur, Indu Ramachandra Rao, Dharshan Rangaswamy and Srinivas Vinayak Shenoy.

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Project administration: Dharshan Rangaswamy, Srinivas Vinayak Shenoy, Shankar Prasad Nagaraju.

Resources: Shilna Muttickal Swaminathan, Indu Ramachandra Rao Srinivas Vinayak Shenoy, and Dharshan Rangaswamy.

Software: Shilna Muttickal Swaminathan, Indu Ramachandra Rao, Srinivas Vinayak Shenoy, and Dharshan Rangaswamy.

Supervision: Shankar Prasad Nagaraju, Mohan V Bhojaraja, and Ravindra Prabhu Attur.

Validation: Shankar Prasad Nagaraju, Mohan V Bhojaraja, Ravindra Prabhu Attur, Indu Ramachandra Rao, and Dharshan Rangaswamy.

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Writing–original draft: Shilna Muttickal Swaminathan, Mohan V Bhojaraja, Indu Ramachandra Rao.

Writing–review & editing: Shankar Prasad Nagaraju, Dharshan Rangaswamy, Ravindra Prabhu Attur and Srinivas Vinayak Shenoy.

Conflicts of interest

The authors declared no competing interests.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by approved by Kasturba Medical College and Kasturba Hospital Institutional Ethics Committee (#IEC-126). Accordingly, written informed consent was taken from all participants before any intervention. The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

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References

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119. doi: 10.1016/j.diabres.2021.109119.
2. Qin C, Wang Y, Zhao L, Zhang J, Ren H, Zou Y, et al. Clinical and Pathological Features of Chinese Patients with Type 2 Diabetes, Biopsy-Proven Diabetic Kidney Disease, and Rapid eGFR Decline. Diabetes Metab Syndr Obes. 2022;15:2847-2856. doi: 10.2147/DMSO.S381052
3. Rabkin R. Diabetic nephropathy. Clin Cornerstone. 2003;5:1-11. doi: 10.1016/s1098-3597(03)90014-7.
4. Zoppini G, Targher G, Chonchol M, Ortalda V, Negri C, Stoico V, et al. Predictors of estimated GFR decline in patients with type 2 diabetes and preserved kidney function. Clin J Am Soc Nephrol. 2012;7:401-8. doi: 10.2215/CJN.07650711.
5. Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, et al. Renal Pathology Society. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010;21:556-63. doi: 10.1681/ASN.2010010010.
6. Osterby R, Gall MA, Schmitz A, Nielsen FS, Nyberg G, Parving HH. Glomerular structure and function in proteinuric type 2 (non-insulin-dependent) diabetic patients. Diabetologia. 1993;36:1064-70. doi: 10.1007/BF02374500.
7. Ruggenenti P, Gambara V, Perna A, Bertani T, Remuzzi G. The nephropathy of non-insulin-dependent diabetes: predictors of outcome relative to diverse patterns of renal injury. J Am Soc Nephrol. 1998;9:2336-43. doi: 10.1681/ASN.V9122336.
8. Bohle AM, Wehrmann M, Bogenschütz O, Batz C, Müller GA. The pathogenesis of chronic renal failure in diabetic nephropathy: investigation of 488 cases of diabetic glomerulosclerosis. Pathology-Research and Practice. 1991;187:251-9.
9. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. Chronic Kidney Disease Epidemiology Collaboration. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385:1737-1749. doi: 10.1056/NEJMoa2102953.
10. Levey AS, Coresh J, Bolton K, Culleton B, Harvey KS, Ikizler TA, et al. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1-266.
11. Misra PS, Szeto SG, Krizova A, Gilbert RE, Yuen DA. Renal histology in diabetic nephropathy predicts progression to end-stage kidney disease but not the rate of renal function decline. BMC Nephrol. 2020;21:285. doi: 10.1186/s12882-020-01943-1.
12. Abbasi MA, Chertow GM, Hall YN. End-stage renal disease. BMJ Clin Evid. 2010;2010:2002.
13. Lemley KV. A basis for accelerated progression of diabetic nephropathy in Pima Indians. Kidney Int Suppl. 2003; S38-42. doi: 10.1046/j.1523-1755.63.s83
14. Yaqub S, Hamid A, Kashif W, Razzaque MR, Farooque A, Ahmed B, et al. Rapidly progressive diabetic kidney disease: South Asian experience. Intern Journal of Diabetes in Developing Countries. 2022:1-8.doi.10.1007/s13410-021-00975-z.
15. Krolewski AS, Skupien J, Rossing P, Warram JH. Fast renal decline to end-stage renal disease: an unrecognized feature of nephropathy in diabetes. Kidney Int. 2017;91:1300-1311. doi: 10.1016/j.kint.2016.10.046.
16. Wang Y, Zhao L, Zhang J, Wu Y, Zhang R, Li H, et al. Implications of a family history of diabetes and rapid egfr decline in patients with type 2 diabetes and biopsy-proven

diabetic kidney disease. Front Endocrinol (Lausanne). 2019;10:855. doi: 10.3389/fendo.2019.00855.
17. Moriya T, Tanaka S, Sone H, Ishibashi S, Matsunaga S, Ohashi Y, et al. Patients with type 2 diabetes having higher glomerular filtration rate showed rapid renal function decline followed by impaired glomerular filtration rate: Japan Diabetes Complications Study. J Diabetes Complications. 2017;31:473-478. doi: 10.1016/j.jdiacomp.2016.06.020.
18. Perkovic V, Heerspink HL, Chalmers J, Woodward M, Jun M, Li Q, et al. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. Kidney Intern. 2013;83:517-23. doi:10.1038/ki.2012.401
19. Lim CT, Nordin NZ, Fadhlina NZ, Anim MS, Kalaiselvam T, Haikal WZ, et al. Rapid decline of renal function in patients with type 2 diabetes with heavy proteinuria: a report of three cases. BMC Nephrol. 2019;20:1-6. doi:10.1186/S12882-019-1203-7.
20. Furuichi K, Shimizu M, Yamanouchi M, Hoshino J, Sakai N, Iwata Y, et al. Clinicopathological features of fast eGFR decliners among patients with diabetic nephropathy. BMJ Open Diabetes Research and Care. 2020;8:e001157.doi: 10.1136/bmjdrc-2019-001157.
21. Okada T, Nagao T, Matsumoto H, Nagaoka Y, Wada T, Nakao T. Histological predictors for renal prognosis in diabetic nephropathy in diabetes mellitus type 2 patients with overt proteinuria. Nephrology. 2012;17:68-75. doi: 10.1111/j.1440-1797.2011.01525.x.
22. An Y, Xu F, Le W, Ge Y, Zhou M, Chen H, et al. Renal histologic changes and the outcome in patients with diabetic nephropathy. Nephrology Dialysis Transplantation. 2015;30:257-66. doi: 10.1093/ndt/gfu250.