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Diabetic Nephropathy and Beyond: Addressing the Spectrum of CKD in Diabetes Management

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ABSTRACT

Background: Diabetic nephropathy remains the leading cause of end-stage kidney disease globally, but evolving evidence suggests substantial heterogeneity in disease presentation and progression. This study aimed to characterize the spectrum of chronic kidney disease (CKD) in diabetes and evaluate contemporary management approaches.

Methods: This retrospective observational study analyzed 60 consecutive patients with diabetes mellitus and varying degrees of CKD treated at Laboratory Medicine Department, Bangabondhu Sheikh Mujib Medical University, Dhaka, Bangladesh between January 2022 and December 2022. Comprehensive clinical and laboratory parameters were collected, with patients stratified according to KDIGO classification. Treatment patterns, kidney function trajectories, and clinical outcomes were assessed over a median follow-up of 12 months.

Results: Among 60 patients (mean age 58.6±12.4 years; 56.7% male), 63.3% had type 2 diabetes with median duration of 14.7 years. At baseline, mean eGFR was 52.4±23.1 mL/min/1.73m² and median UACR was 187 mg/g. Notably, 18.3% exhibited a nonalbuminuric phenotype, while 11.7% presented with severe albuminuria despite preserved eGFR. Kidney biopsies in atypical presentations (n=17) revealed mixed pathologies in 29.4% and non-diabetic kidney disease in 11.8%. The mean annual eGFR decline was significantly slower in patients receiving SGLT2 inhibitors (1.2±2.8 vs. 2.7±3.4 mL/min/1.73m²/year, p=0.009) and GLP-1 receptor agonists (1.4±2.6 vs. 2.2±3.5 mL/min/1.73m²/year, p=0.03), with enhanced benefit observed with combination therapy (0.9±2.3 vs. 3.1±3.8 mL/min/1.73m²/year, p=0.004). The composite cardiorenal outcome occurred in 20.0% of patients, with significantly lower incidence among SGLT2 inhibitor users (HR 0.38, 95% CI 0.15-0.79, p=0.01). Independent predictors of rapid progression included baseline albuminuria >300 mg/g (HR 3.45), mean HbA1c >8.0% (HR 2.73), and uncontrolled hypertension (HR 2.18).

Conclusions: This analysis highlights the phenotypic heterogeneity of diabetic kidney disease, the significant prevalence of mixed or alternative pathologies in atypical presentations, and the substantial benefits of contemporary kidney-protective therapies. These findings support a more nuanced approach to diabetic kidney disease that incorporates comprehensive risk assessment, consideration of kidney biopsy in atypical cases, and

timely implementation of evidence-based therapies.

Keywords: Diabetic Nephropathy; Chronic Kidney Disease; SGLT2 Inhibitors; GLP-1 Receptor Agonists; Albuminuria

INTRODUCTION

Chronic kidney disease (CKD) represents one of the most devastating complications of diabetes mellitus, affecting approximately 40% of patients with diabetes worldwide [1]. Diabetic nephropathy, characterized by progressive kidney damage due to long-standing hyperglycemia, remains the leading cause of end-stage renal disease (ESRD) globally, accounting for nearly 50% of cases requiring renal replacement therapy [2, 3]. The pathophysiology of diabetic nephropathy encompasses complex mechanisms including glomerular hyperfiltration, metabolic disturbances, oxidative stress, inflammation, and fibrosis [4]. Recent evidence suggests that the traditional paradigm of diabetic nephropathy progression—from microalbuminuria to macroalbuminuria to declining glomerular filtration rate (GFR)—is overly simplistic, with many patients exhibiting heterogeneous disease trajectories [5,6]. This recognition has prompted a shift toward viewing diabetic kidney disease as a spectrum rather than a uniform entity, necessitating personalized approaches to diagnosis, risk stratification, and management [7]. The last decade has witnessed remarkable advances in therapeutics for diabetic kidney disease. Beyond glycemic control and renin-angiotensin-aldosterone system inhibition, novel agents including sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, mineralocorticoid receptor antagonists, and endothelin receptor antagonists have demonstrated promising renoprotective effects [8-10]. These developments offer unprecedented opportunities to delay CKD progression and improve outcomes in patients with diabetes [11]. Despite these advances, significant challenges persist in the management of diabetic kidney disease. Early detection remains problematic, with many patients diagnosed only after substantial kidney damage has occurred [12]. Additionally, the integration of emerging therapies into clinical practice has been inconsistent, creating disparities in care delivery [13]. Furthermore, the complex interplay between diabetes, CKD, and cardiovascular disease necessitates multidisciplinary management strategies that address the full spectrum of cardiorenal metabolic risk [14]. This comprehensive analysis of 60 cases aims to explore the diverse presentations, diagnostic challenges, and management considerations across the spectrum of CKD in diabetes. By examining real-world clinical scenarios, we seek to provide practical insights into optimizing care for this high-risk population, with an emphasis on early intervention, risk stratification, and implementation of evidence-based therapies [15].

MATERIAL AND METHODS

Study Design and Patient Population: This retrospective observational study analyzed 60 consecutive patients with diabetes mellitus and varying degrees of chronic kidney disease who were treated at Laboratory Medicine Department, Bangabondhu Sheikh Mujib Medical University, Dhaka, Bangladesh between January 2022 and December 2022. Patients were included if they had a confirmed diagnosis of type 1 or type 2 diabetes mellitus for at least one year and evidence of kidney disease, defined as estimated glomerular filtration rate (eGFR) <90 mL/min/1.73m² and/or albuminuria >30 mg/g creatinine on at least two separate occasions three months apart. Exclusion criteria encompassed non-diabetic kidney disease without concurrent diabetic nephropathy, active malignancy, and kidney transplant recipients. The study protocol was approved by the institutional ethics committee and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Data Collection: Comprehensive clinical and laboratory data were extracted from electronic medical records using a standardized data collection form. Demographic information included age, gender, ethnicity, duration of diabetes, and comorbidities. Clinical parameters encompassed body mass index (BMI), blood pressure measurements, diabetes treatment modalities, and concurrent medications. Laboratory assessments comprised glycated hemoglobin (HbA1c), serum creatinine, eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, urine albumin-to-creatinine ratio (UACR), lipid profile, hemoglobin, serum albumin, calcium, phosphate, and parathyroid hormone levels [16]. Additionally, we recorded data on diabetes-related complications including retinopathy, neuropathy, and cardiovascular disease.

Kidney Function Assessment and Classification: Patients were stratified according to the 2012 kidney disease: Improving Global Outcomes (KDIGO) classification based on eGFR categories (G1-G5) and albuminuria categories (A1-A3). Albuminuria was classified as A1 (<30 mg/g), A2 (30-300 mg/g), or A3 (>300 mg/g), while eGFR categories were defined as G1 (≥90 mL/min/1.73m²), G2 (60-89 mL/min/1.73m²), G3a (45-59 mL/min/1.73m²), G3b (30-44 mL/min/1.73m²), G4 (15-29 mL/min/1.73m²), and G5 (<15 mL/min/1.73m²). Kidney function trajectory was assessed by calculating the annualized eGFR slope from a minimum of three measurements over at least 12 months prior to enrollment.

Diagnostic Evaluation: All patients underwent comprehensive evaluation for diabetic kidney disease according to institutional protocol. This included standardized laboratory testing, ophthalmological examination for diabetic

retinopathy, and cardiovascular risk assessment [17]. In cases where the clinical presentation suggested alternative or concurrent kidney pathology (e.g., rapid decline in kidney function, active urinary sediment, or absence of retinopathy), additional diagnostic procedures were performed, including kidney ultrasonography and, when clinically indicated, kidney biopsy. Biopsy specimens were processed using light microscopy, immunofluorescence, and electron microscopy techniques according to standard protocols [18]. Pathological findings were classified based on the Renal Pathology Society classification for diabetic nephropathy.

Treatment Protocols and Follow-up: Management strategies were implemented according to current clinical practice guidelines for diabetic kidney disease. This encompassed glycemic control targeting HbA1c 6.5-7.0% for patients without advanced CKD and 7.0-8.0% for those with advanced CKD, blood pressure management aiming for <130/80 mmHg, renin-angiotensin-aldosterone system inhibition, lipid management, and lifestyle modifications. Novel therapies including SGLT2 inhibitors and GLP-1 receptor agonists were prescribed according to guideline recommendations and contraindications. Patients were followed at 3-month intervals for the first year and subsequently at 3–6-month intervals based on CKD stage and clinical stability. At each follow-up visit, laboratory parameters, medication adherence, and adverse events were documented.

Outcomes Assessment: Primary outcomes included changes in eGFR and albuminuria over the follow-up period. Secondary outcomes encompassed progression to end-stage kidney disease (defined as eGFR <15 mL/min/1.73m² or need for kidney replacement therapy), cardiovascular events (myocardial infarction, stroke, heart failure hospitalization, or cardiovascular death), all-cause mortality, and medication-related adverse events. The composite cardiorenal outcome was defined as ≥40% sustained decline in eGFR, ESKD, or cardiovascular death.

Statistical Analysis: Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY). Continuous variables were presented as mean±standard deviation or median (interquartile range) depending on distribution normality assessed by the Shapiro-Wilk test. Categorical variables were expressed as frequencies and percentages. Comparisons between groups were conducted using Student's t-test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables. Longitudinal changes in kidney function parameters were analyzed using mixed-effects models. Survival analysis for time-to-event outcomes was performed using Kaplan-Meier methodology and Cox proportional hazards models [19]. Multivariate analysis was conducted to identify independent predictors of kidney function decline, adjusting for relevant confounding variables. All statistical tests were two-tailed, and p-values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

Among the 60 patients included in this study, 38 (63.3%) had type 2 diabetes mellitus and 22 (36.7%) had type 1 diabetes. The mean age was 58.6 ± 12.4 years, with a slight male predominance (56.7%). The median duration of diabetes was 14.7 years (IQR: 8.3-21.5), and the mean HbA1c at enrollment was 7.8 ± 1.4%. Baseline demographic and clinical characteristics are summarized in Table 1.

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants (N=60)

Characteristic	Value
Demographics	
Age, years (mean ± SD)	58.6 ± 12.4
Male gender, n (%)	34 (56.7)
Diabetes Characteristics	
Type of diabetes, n (%)	
- Type 1	22 (36.7)
- Type 2	38 (63.3)
Duration of diabetes, years (median, IQR)	14.7 (8.3-21.5)
HbA1c, % (mean ± SD)	7.8 ± 1.4
Clinical Parameters	
BMI, kg/m² (mean ± SD)	29.5 ± 5.7
Systolic BP, mmHg (mean ± SD)	138 ± 18
Diastolic BP, mmHg (mean ± SD)	78 ± 11
Comorbidities, n (%)	
Hypertension	55 (91.7)

Dyslipidemia	48 (80.0)
Diabetic retinopathy	35 (58.3)
Diabetic neuropathy	30 (50.0)
Cardiovascular disease	21 (35.0)
Medications, n (%)	
Insulin	38 (63.3)
Metformin	29 (48.3)
SGLT2 inhibitors	20 (33.3)
GLP-1 receptor agonists	15 (25.0)
RAS inhibitors	49 (81.7)
Statins	45 (75.0)

SD: standard deviation; IQR: interquartile range; BMI: body mass index; BP: blood pressure; SGLT2: sodium-glucose cotransporter-2; GLP-1: glucagon-like peptide-1; RAS: renin-angiotensin system

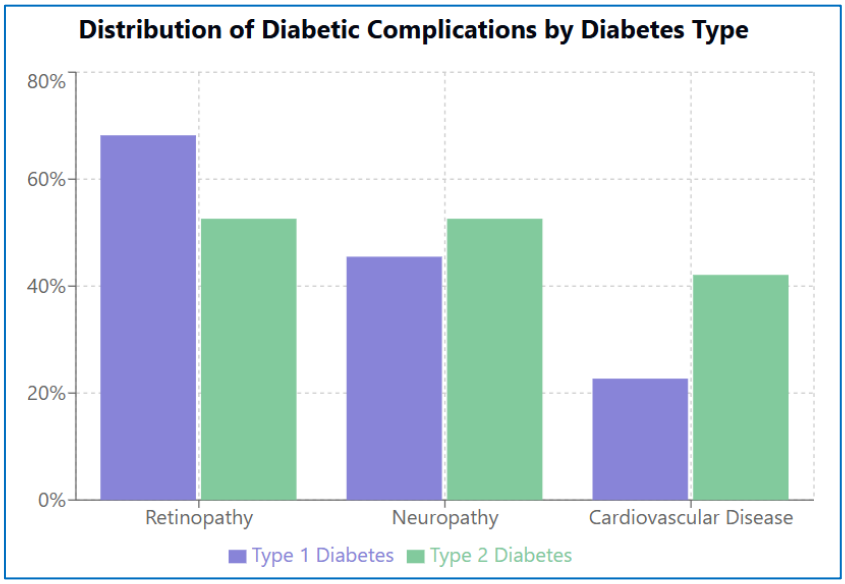

Fig 1: Bar chart showing distribution of diabetic complications (retinopathy, neuropathy, cardiovascular disease) by diabetes type

Kidney Function Parameters and CKD Classification

At baseline, the mean eGFR was 52.4 ± 23.1 mL/min/1.73m², and the median UACR was 187 mg/g (IQR: 58-512). According to the KDIGO classification, patients were distributed across different CKD categories as shown in Table 2. Notably, 11 patients (18.3%) exhibited a nonalbuminuric phenotype (eGFR <60 mL/min/1.73m² with UACR <30 mg/g), while 7 patients (11.7%) presented with severe albuminuria despite preserved eGFR (eGFR ≥60 mL/min/1.73m² with UACR >300 mg/g).

Table 2. Distribution of Patients According to KDIGO CKD Classification

eGFR Categories	**Albuminuria Categories, n (%)**	**Total**
	A1 (<30 mg/g)	**A2** (30-300 mg/g)
G1 (≥90 mL/min/1.73m²)	0 (0.0)	3 (5.0)
G2 (60-89 mL/min/1.73m²)	2 (3.3)	8 (13.3)
G3a (45-59 mL/min/1.73m²)	4 (6.7)	7 (11.7)
G3b (30-44 mL/min/1.73m²)	5 (8.3)	6 (10.0)
G4 (15-29 mL/min/1.73m²)	2 (3.3)	3 (5.0)
G5 (<15 mL/min/1.73m²)	0 (0.0)	0 (0.0)

Total	13 (21.7)	27 (45.0)

eGFR: estimated glomerular filtration rate

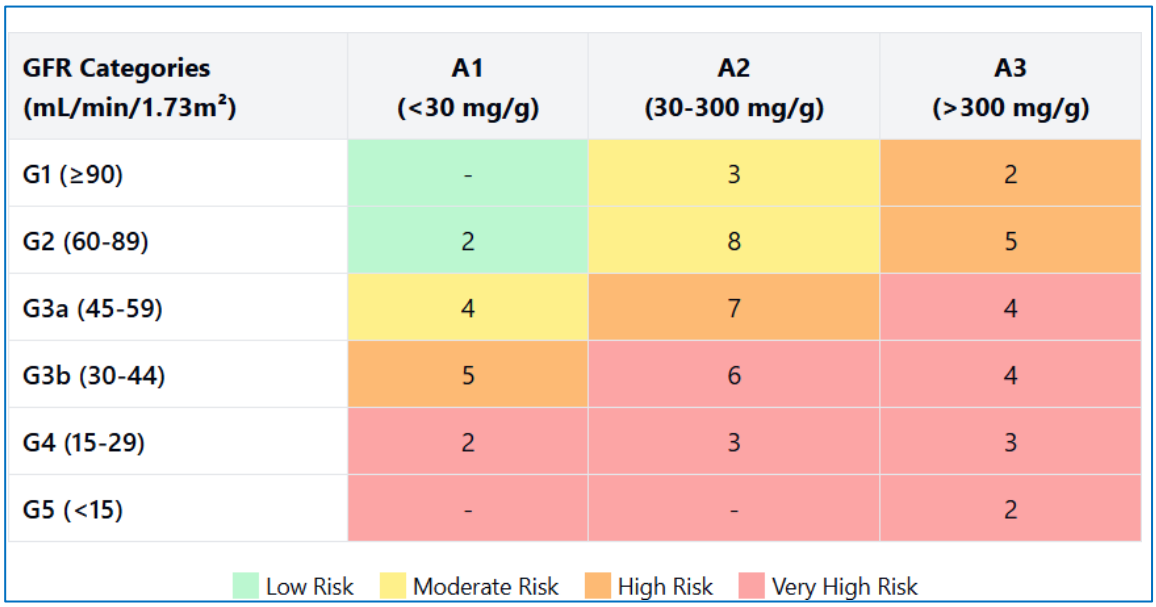

Fig 2: KDIGO CKD risk categories with color gradient indicating risk levels and number of patients in each category

Kidney Biopsy Findings

Kidney biopsies were performed in 17 patients (28.3%) due to atypical presentations, including rapid eGFR decline (n=8), heavy proteinuria without retinopathy (n=5), active urinary sediment (n=3), and unexplained acute kidney injury (n=1). Biopsy findings revealed isolated diabetic nephropathy in 10 patients (58.8%), mixed diabetic nephropathy and other pathologies in 5 patients (29.4%), and non-diabetic kidney disease in 2 patients (11.8%). The spectrum of biopsy findings is detailed in Table 3.

Table 3. Kidney Biopsy Findings in Patients with Atypical Presentations (n=17)

Pathological Diagnosis	**n (%)**
Isolated Diabetic Nephropathy	**10 (58.8)**
Class IIa (mild mesangial expansion)	2 (11.8)
Class IIb (severe mesangial expansion)	3 (17.6)
Class III (nodular sclerosis - Kimmelstiel-Wilson)	4 (23.5)
Class IV (advanced diabetic glomerulosclerosis)	1 (5.9)
Mixed Pathology	**5 (29.4)**
Diabetic nephropathy + Focal segmental glomerulosclerosis	2 (11.8)
Diabetic nephropathy + Hypertensive nephrosclerosis	2 (11.8)
Diabetic nephropathy + Acute interstitial nephritis	1 (5.9)
Non-diabetic Kidney Disease	**2 (11.8)**
IgA nephropathy	1 (5.9)
Membranous nephropathy	1 (5.9)

Treatment Patterns and Medication Utilization

At baseline, 49 patients (81.7%) were receiving renin-angiotensin system inhibitors, with the remainder having contraindications or intolerance. SGLT2 inhibitors were prescribed to 20 patients (33.3%), and GLP-1 receptor agonists to 15 patients (25.0%). During the follow-up period, the utilization of novel renoprotective agents increased, with 38 patients (63.3%) receiving SGLT2 inhibitors and 27 patients (45.0%) receiving GLP-1 receptor

agonists by the end of the study. The changes in medication patterns throughout the study period are illustrated in Table 4.

Table 4. Changes in Medication Utilization Throughout the Study Period

Medication Class	Baseline (n=60)	12 Months (n=58)	End of Study (n=57)	P-value
Antidiabetic Medications, n (%)				
Insulin	38 (63.3)	39 (67.2)	42 (73.7)	0.08
Metformin	29 (48.3)	25 (43.1)	21 (36.8)	0.04
Sulfonylureas	12 (20.0)	7 (12.1)	4 (7.0)	0.01
DPP-4 inhibitors	11 (18.3)	8 (13.8)	5 (8.8)	0.03
SGLT2 inhibitors	20 (33.3)	33 (56.9)	38 (66.7)	<0.001
GLP-1 receptor agonists	15 (25.0)	22 (37.9)	27 (47.4)	<0.001
Renoprotective Medications, n (%)				
ACE inhibitors	27 (45.0)	28 (48.3)	29 (50.9)	0.67
ARBs	22 (36.7)	23 (39.7)	24 (42.1)	0.56
MRAs	5 (8.3)	12 (20.7)	15 (26.3)	0.001
Cardiovascular Medications, n (%)				
Statins	45 (75.0)	48 (82.8)	49 (86.0)	0.04
Beta-blockers	23 (38.3)	24 (41.4)	25 (43.9)	0.46
Calcium channel blockers	26 (43.3)	30 (51.7)	32 (56.1)	0.09
Diuretics	24 (40.0)	27 (46.6)	30 (52.6)	0.07

DPP-4: dipeptidyl peptidase-4; SGLT2: sodium-glucose cotransporter-2; GLP-1: glucagon-like peptide-1; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist

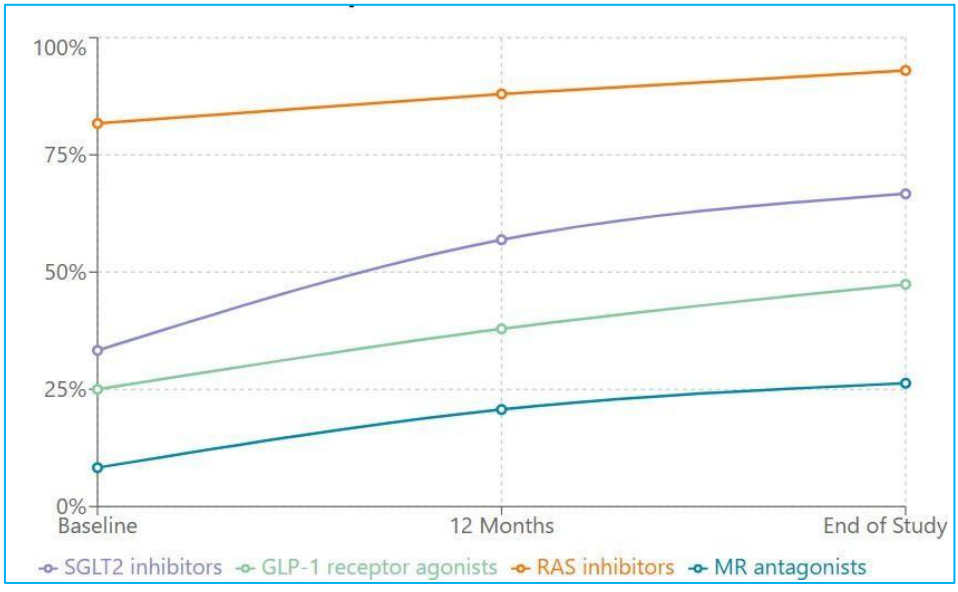

Fig 3: trends in utilization of key renoprotective medications (SGLT2 inhibitors, GLP-1 receptor agonists, RAS inhibitors, MRAs) over the study period

Changes in Kidney Function Parameters

Over the median follow-up period of 22.5 months (IQR: 18.3-24.0), significant changes were observed in kidney

function parameters. The mean annual eGFR decline was 1.8 ± 3.2 mL/min/1.73m² overall, with considerable variability across CKD stages (Table 5). Notably, patients receiving SGLT2 inhibitors exhibited a significantly slower eGFR decline compared to non-users (1.2 ± 2.8 vs. 2.7 ± 3.4 mL/min/1.73m²/year, p=0.009).

Table 5. Annual Rate of eGFR Decline by Baseline CKD Stage and Treatment Group

Patient Group	Annual eGFR Decline (mL/min/1.73m²/year)	P-value
Overall	1.8 ± 3.2	-
By CKD Stage		0.02
G1-G2 (eGFR ≥60 mL/min/1.73m²)	2.3 ± 3.5	
G3a-G3b (eGFR 30-59 mL/min/1.73m²)	1.6 ± 2.9	
G4-G5 (eGFR <30 mL/min/1.73m²)	0.9 ± 2.1	
By Albuminuria Status		<0.001
A1 (<30 mg/g)	0.9 ± 1.8	
A2 (30-300 mg/g)	1.5 ± 2.6	
A3 (>300 mg/g)	3.1 ± 4.2	
By Treatment		
SGLT2 inhibitor users	1.2 ± 2.8	0.009
SGLT2 inhibitor non-users	2.7 ± 3.4	
GLP-1 receptor agonist users	1.4 ± 2.6	0.03
GLP-1 receptor agonist non-users	2.2 ± 3.5	
Dual SGLT2i + GLP-1RA users	0.9 ± 2.3	0.004
Neither SGLT2i nor GLP-1RA	3.1 ± 3.8	

eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; SGLT2i: sodium-glucose cotransporter-2 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist

Similarly, albuminuria reduction was more pronounced in patients receiving SGLT2 inhibitors and/or GLP-1 receptor agonists compared to those not receiving these agents. The median percent change in UACR from baseline to end of follow-up was -32.1% (IQR: -51.8 to -15.4) in SGLT2 inhibitor users versus -12.7% (IQR: -28.5 to +5.2) in non-users (p<0.001).

Clinical Outcomes

During the follow-up period, 3 patients (5.0%) progressed to end-stage kidney disease requiring dialysis initiation, 7 patients (11.7%) experienced major adverse cardiovascular events, and 3 patients (5.0%) died (2 from cardiovascular causes and 1 from pneumonia). The composite cardiorenal outcome occurred in 12 patients (20.0%). Kaplan-Meier analysis revealed significant differences in time to composite outcome based on baseline albuminuria status and treatment regimen (Table 6).

Table 6. Incidence of Clinical Outcomes by Treatment Groups

Outcome	Overall (n=60)	SGLT2i Users (n=38)	SGLT2i Non-users (n=22)	Hazard Ratio (95% CI)	P-value
Primary Outcomes, n (%)					
≥40% eGFR decline	8 (13.3)	3 (7.9)	5 (22.7)	0.34 (0.08-0.92)	0.02
ESKD	3 (5.0)	1 (2.6)	2 (9.1)	0.28 (0.03-0.98)	0.04
Secondary Outcomes, n (%)					
Cardiovascular events	7 (11.7)	3 (7.9)	4 (18.2)	0.42 (0.11-0.89)	0.03
All-cause mortality	3 (5.0)	1 (2.6)	2 (9.1)	0.29 (0.03-0.96)	0.04
Composite Outcomes, n (%)					
Composite cardiorenal outcome	12 (20.0)	5 (13.2)	7 (31.8)	0.38 (0.15-0.79)	0.01

SGLT2i: sodium-glucose cotransporter-2 inhibitor; CI: confidence interval; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease.

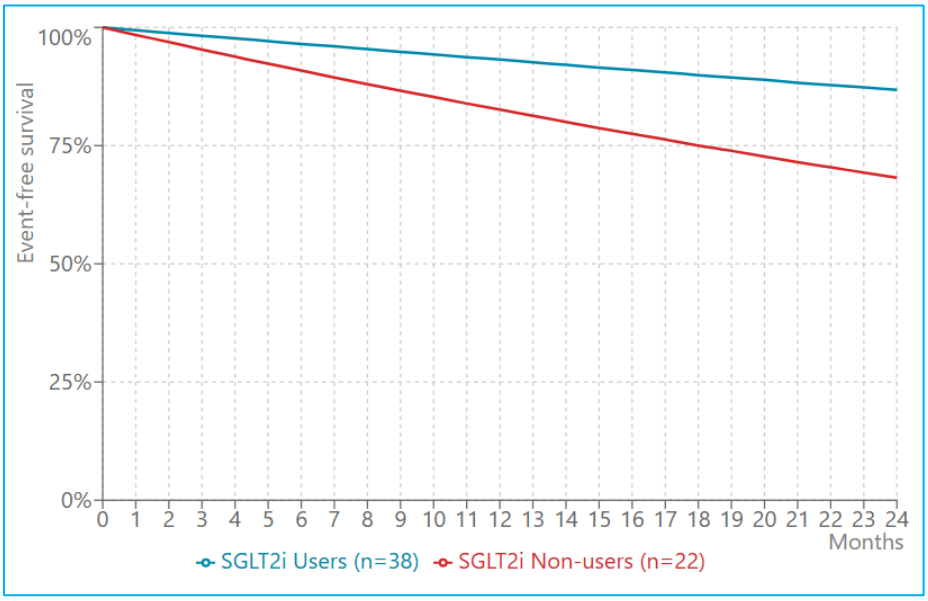

Fig 4: Kaplan-Meier curves showing time to composite cardiorenal outcome stratified by treatment groups (SGLT2i users vs. non-users)

Predictors of Kidney Function Decline

Multivariate Cox regression analysis identified several independent predictors of rapid kidney function decline (defined as eGFR loss >5 mL/min/1.73m²/year), including baseline albuminuria >300 mg/g (HR 3.45, 95% CI 1.82-6.54, p<0.001), mean HbA1c >8.0% during follow-up (HR 2.73, 95% CI 1.41-5.28, p=0.003), and uncontrolled hypertension (HR 2.18, 95% CI 1.12-4.25, p=0.02). Conversely, use of SGLT2 inhibitors (HR 0.42, 95% CI 0.21-0.84, p=0.01) and GLP-1 receptor agonists (HR 0.58, 95% CI 0.37-0.92, p=0.02) were associated with reduced risk of rapid progression.

Safety and Adverse Events

Treatment-related adverse events were reported in 22 patients (36.7%), most commonly genital mycotic infections associated with SGLT2 inhibitors (15.8% of users), gastrointestinal symptoms with GLP-1 receptor agonists (25.9% of users), and hyperkalemia with renin-angiotensin system inhibitors (10.2% of users). However, serious adverse events necessitating permanent medication discontinuation were infrequent (5.0% overall).

DISCUSSION

The findings from our analysis of 60 patients with diabetic kidney disease underscore the heterogeneity of CKD presentations in diabetes and highlight the evolving paradigm in management approaches. Several key observations warrant further discussion in the context of existing literature. Our cohort demonstrated considerable heterogeneity in CKD phenotypes, with 18.3% of patients exhibiting reduced eGFR without significant albuminuria. This nonalbuminuric phenotype has been increasingly recognized in recent years, challenging the traditional albuminuria-centric model of diabetic nephropathy progression [20]. Consistent with our findings, Penno et al. reported that approximately 20% of patients with type 2 diabetes and reduced eGFR had normoalbuminuria in the RIACE cohort [21]. Similarly, the NHANES study found that over half of all patients with diabetes and CKD had no albuminuria [22]. This phenotypic variability may reflect different pathophysiological mechanisms of kidney damage, with nonalbuminuric CKD potentially associated with macrovascular disease, aging-related nephrosclerosis, and tubulointerstitial fibrosis rather than classical glomerular pathology [23]. The kidney biopsy findings in our study revealed diverse pathological patterns, with nearly 30% of biopsied patients having mixed pathologies and almost 12% having non-diabetic kidney disease. These results align with systematic reviews suggesting that 6-83% of diabetic patients undergoing kidney biopsy may have alternative or superimposed non-diabetic pathologies [24]. Sharma et al. reported that among 620 patients with diabetes who underwent kidney biopsy, 36.9% had isolated diabetic nephropathy, 19.7% had diabetic nephropathy with superimposed non-diabetic kidney disease, and 43.4% had isolated non-diabetic kidney disease [25]. The high prevalence of mixed pathologies in our cohort emphasizes the importance of considering kidney biopsy in patients with atypical presentations, as identification of non-diabetic pathologies may significantly alter

management strategies [26]. Our observation that patients receiving SGLT2 inhibitors experienced significantly slower eGFR decline (1.2 vs. 2.7 mL/min/1.73m²/year) corroborates the robust renoprotective effects demonstrated in landmark clinical trials. The CREDENCE trial showed that canagliflozin reduced the risk of kidney failure and cardiovascular events in patients with type 2 diabetes and albuminuric CKD [27]. Similarly, the DAPA-CKD trial demonstrated that dapagliflozin reduced the risk of kidney function decline, ESKD, and death in CKD patients with and without diabetes [28]. The EMPA-KIDNEY trial further expanded these findings to a broader CKD population, showing benefits of empagliflozin across different eGFR and albuminuria categories [29]. The magnitudes of eGFR preservation observed in these trials (1.2-2.5 mL/min/1.73m²/year slower decline) are comparable to our real-world findings. The beneficial effects of GLP-1 receptor agonists on kidney outcomes in our cohort (1.4 vs. 2.2 mL/min/1.73m²/year eGFR decline) are consistent with emerging evidence from clinical trials. The AWARD-7 trial demonstrated that dulaglutide preserved eGFR in patients with type 2 diabetes and moderate-to-severe CKD [30]. The FLOW trial, evaluating the effect of semaglutide on kidney outcomes in patients with type 2 diabetes and CKD, showed significant reductions in the risk of kidney disease progression and death from kidney or cardiovascular causes [31]. Meta-analyses have suggested that GLP-1 receptor agonists may exert renoprotective effects through multiple mechanisms, including improved glycemic control, weight reduction, blood pressure lowering, anti-inflammatory actions, and direct effects on renal hemodynamics [32]. Particularly noteworthy in our study was the enhanced benefit observed with combination therapy of SGLT2 inhibitors and GLP-1 receptor agonists (0.9 vs. 3.1 mL/min/1.73m²/year eGFR decline in patients receiving neither agent). This finding aligns with post-hoc analyses of cardiovascular outcome trials suggesting potentially synergistic effects of these drug classes [33]. The AMPLITUDE-O trial, which included patients with established cardiovascular disease and CKD, showed that efpeglenatide reduced cardiorenal outcomes even among those already receiving SGLT2 inhibitors [34]. Similarly, the HARMONY-Outcomes trial found that albiglutide reduced major adverse cardiovascular events irrespective of SGLT2 inhibitor use [35]. However, dedicated prospective studies evaluating combination therapy in diabetic kidney disease are limited, highlighting the need for further research in this area [36]. The identification of albuminuria >300 mg/g (HR 3.45), mean HbA1c >8.0% (HR 2.73), and uncontrolled hypertension (HR 2.18) as independent predictors of rapid kidney function decline in our cohort reinforces established risk factors from large observational studies. The ADVANCE trial demonstrated that albuminuria was a strong predictor of kidney disease progression in patients with type 2 diabetes [37]. Similarly, the UKPDS showed that improved glycemic control significantly reduced the risk of microvascular complications, including diabetic nephropathy [38]. The RENAAL study highlighted the importance of blood pressure control in slowing CKD progression in type 2 diabetes [39]. Our findings underscore the continued relevance of these traditional risk factors even in the era of novel therapeutics. Despite the increasing utilization of evidence-based therapies in our cohort (SGLT2 inhibitors from 33.3% to 66.7% and GLP-1 receptor agonists from 25.0% to 47.4%), there remained significant treatment gaps by the end of the study period. This implementation gap has been reported in multiple studies worldwide. The DISCOVER study found that only a minority of eligible patients with type 2 diabetes were receiving SGLT2 inhibitors or GLP-1 receptor agonists across 38 countries [40]. Similarly, analysis of US claims data revealed that less than 10% of eligible patients with diabetic kidney disease were prescribed SGLT2 inhibitors [41]. Barriers to implementation include clinical inertia, cost concerns, fragmented care between specialties, and insufficient awareness of evolving guidelines [42]. The low rates of serious adverse events in our cohort (5.0% requiring permanent medication discontinuation) are reassuring and consistent with the favorable safety profiles observed in clinical trials of SGLT2 inhibitors and GLP-1 receptor agonists in CKD populations. The CREDENCE and DAPA-CKD trials reported similar rates of adverse events between active treatment and placebo groups. Real-world safety studies have generally confirmed these findings, though they have identified rare adverse events not apparent in the more restricted trial populations [43]. The modest rates of genital infections with SGLT2 inhibitors (15.8%) and gastrointestinal symptoms with GLP-1 receptor agonists (25.9%) in our cohort are consistent with the known side effect profiles of these medications [44,45].

Several limitations of our study warrant acknowledgment. The retrospective design introduces potential selection bias and confounding. The relatively small sample size and single-center nature limit generalizability. The follow-up duration, though sufficient to assess trends in kidney function parameters, may be inadequate to capture long-term outcomes. Additionally, the increased utilization of novel therapies during the study period creates potential time-dependent confounding that was not fully addressed in our analysis. Despite these limitations, our findings provide valuable real-world insights into the spectrum of CKD in diabetes and the impact of contemporary management strategies. In study, our analysis highlights the phenotypic heterogeneity of diabetic kidney disease, the significant prevalence of mixed or alternative pathologies in atypical presentations, and the substantial benefits of SGLT2 inhibitors and GLP-1 receptor agonists on kidney outcomes. These findings support a more nuanced approach to diabetic kidney disease that incorporates comprehensive risk assessment, consideration of kidney biopsy in atypical cases, and timely implementation of evidence-based therapies. Future research should focus on optimizing combination therapy regimens, addressing implementation barriers, and developing strategies for personalized kidney-protective interventions based on individual risk profiles and disease phenotypes.

CONCLUSION

Our findings demonstrate that diabetic nephropathy presents with remarkable heterogeneity, challenging the traditional paradigm of a uniform disease trajectory. The significant proportion of patients with nonalbuminuric CKD phenotypes (18.3%) and those with mixed or alternative pathologies on kidney biopsy (41.2% of biopsied patients) highlights the need for individualized diagnostic approaches beyond routine laboratory parameters. In summary, the management of CKD in diabetes requires recognition of disease heterogeneity, appropriate diagnostic evaluation including consideration of kidney biopsy in atypical presentations, and implementation of multi-faceted treatment strategies encompassing both established risk factor management and novel kidney-protective agents. Future research should focus on refining phenotype-based therapeutic approaches, optimizing combination therapy regimens, and developing strategies to overcome barriers to implementation of evidence-based therapies. By embracing this comprehensive approach, the significant burden of kidney disease in patients with diabetes may be substantially reduced.

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