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Original Research Article

Progression of Diabetic Nephropathy in Patients with Uncontrolled Type 2 Diabetes Mellitus

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Abstract:

Background: Diabetic nephropathy (DN) is a leading cause of end-stage renal disease worldwide, and its progression is strongly linked to glycemic control in type 2 diabetes mellitus (T2DM). While the association is well-established, contemporary data on the rate of renal function decline in patients with persistently poor glycemic control versus those with sustained control are needed to reinforce clinical management strategies.

Methods: A total of 250 patients with T2DM for ≥5 years and a baseline eGFR >60 mL/min/1.73m² were enrolled and stratified into two groups based on baseline and follow-up glycated hemoglobin (HbA1c) levels: an uncontrolled group (n=120; mean HbA1c >8.5%) and a controlled group (n=130; mean HbA1c <7.0%). Annual assessments included eGFR (calculated via the CKD-EPI 2021 equation) and UACR. The primary outcomes were the mean annual rate of eGFR decline and the median change in UACR over 5 years.

Results: At baseline, both groups were comparable in age, sex, and diabetes duration. The uncontrolled group exhibited a significantly greater mean annual eGFR decline (-4.8 ± 1.2 mL/min/1.73m²) compared to the controlled group (-1.6 ± 0.8 mL/min/1.73m²; p<0.001). The median UACR increased from 25 mg/g [IQR 15–40] to 88 mg/g [IQR 45–155] in the uncontrolled group, a significantly greater change than in the controlled group, which increased from 22 mg/g [IQR 14–35] to 31 mg/g [IQR 20–48] (p<0.001). Furthermore, the incidence of a composite renal endpoint (new-onset macroalbuminuria or a >40% sustained eGFR decline) was significantly higher in the uncontrolled cohort (31.7% vs. 6.2%; p<0.001).

Conclusion: Persistent poor glycemic control in patients with T2DM is associated with a three-fold acceleration in the rate of eGFR decline and a substantial increase in albuminuria over a 5-year period. These findings underscore the critical importance of achieving and maintaining long-term glycemic targets to preserve renal function and prevent the progression of diabetic nephropathy.

Keywords: Diabetic Nephropathy, Type 2 Diabetes Mellitus, Glycemic Control, eGFR, Albuminuria, Disease Progression.

Introduction

Type 2 diabetes mellitus (T2DM) has reached pandemic proportions, affecting over 537 million adults globally, with projections indicating a continued rise [1]. Among its most devastating microvascular complications is diabetic nephropathy (DN), also known as diabetic kidney disease (DKD), which stands as the single leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide [2].

The development and progression of DN not only portend a high risk of requiring renal replacement therapy but are also independently associated with a markedly increased risk of cardiovascular morbidity and mortality, imposing a profound burden on patients and healthcare systems [3]. The pathophysiology of DN is complex and multifactorial, driven primarily by chronic hyperglycemia. Sustained high blood glucose levels initiate a cascade of metabolic and hemodynamic derangements within the kidney, including the formation of advanced glycation end-products (AGEs), activation of protein kinase C, increased flux through the polyol pathway, and upregulation of the renin-angiotensin-aldosterone system (RAAS) [4].

These pathways converge to induce glomerular hyperfiltration, oxidative stress, inflammation, and endothelial dysfunction, ultimately leading to structural changes such as glomerular basement membrane thickening, mesangial expansion, and tubulointerstitial fibrosis [4, 5]. Clinically, this damage manifests as a progressive increase in

urinary albumin excretion (albuminuria) and a decline in the estimated glomerular filtration rate (eGFR). The foundational role of glycemic control in mitigating the risk of DN was unequivocally established by the United Kingdom Prospective Diabetes Study (UKPDS). This landmark trial demonstrated that intensive glucose control significantly reduced the incidence of microvascular complications, including nephropathy, in patients with newly diagnosed T2DM [6]. Follow-up studies have further highlighted the concept of a "metabolic legacy," wherein early glycemic control confers long-term renal protection, even if control wanes over time [7]. Conversely, poor glycemic control is a potent and consistent predictor of adverse renal outcomes.

Despite this well-established evidence, a significant proportion of patients with T2DM fail to achieve or maintain recommended glycemic targets, often due to a combination of clinical inertia, treatment non-adherence, and disease complexity [8]. While cross-sectional studies consistently link high HbA1c levels to the presence of DN, there remains a research gap in contemporary, longitudinal data that precisely quantifies the rate of renal function deterioration in real-world patients who remain persistently uncontrolled over several years. Such data are crucial for patient counseling, risk stratification, and reinforcing the urgency of intensive management in this high-risk population.

Therefore, the primary aim of this 5-year prospective study was to evaluate the progression of diabetic nephropathy, as measured by the annual rate of eGFR decline and changes in UACR, in a cohort of patients with persistently uncontrolled T2DM compared to a similar cohort with sustained, guideline-concordant glycemic control.

Materials and Methods

Study Design and Population: Patients were recruited from a dedicated diabetes outpatient clinic. We enrolled adults aged 40–75 years with a confirmed diagnosis of T2DM for at least 5 years.

Inclusion and Exclusion Criteria: Inclusion criteria were: (1) T2DM diagnosed based on American Diabetes Association criteria; (2) age 40–75 years; (3) duration of diabetes ≥5 years; and (4) baseline eGFR ≥60 mL/min/1.73m².

Exclusion criteria included: (1) type 1 diabetes or secondary forms of diabetes; (2) known non-diabetic kidney disease (e.g., glomerulonephritis, polycystic kidney disease); (3) history of kidney transplant; (4) uncontrolled hypertension (systolic blood pressure >160 mmHg or diastolic >100 mmHg despite treatment) at baseline; (5) advanced heart failure (New York Heart Association class III–IV); and (6) active malignancy. Participants were stratified into two groups based on glycemic control status at baseline and maintained during follow-up:

1. **Uncontrolled Group:** Mean HbA1c consistently >8.5% (69 mmol/mol) on at least two measurements in the year prior to enrollment and during annual follow-up.
2. **Controlled Group:** Mean HbA1c consistently <7.0% (53 mmol/mol) over the same period.

Data Collection and Procedures

At baseline and annually for 5 years, all participants underwent a comprehensive clinical and laboratory evaluation. Demographic data, medical history, and medication use (including RAAS inhibitors) were collected. Physical examination included weight, height for BMI calculation (kg/m²), and seated blood pressure (average of two readings).

Venous blood samples were collected after an overnight fast for measurement of HbA1c, serum creatinine, and fasting plasma glucose. First-morning void urine samples were collected for measurement of albumin and creatinine. All laboratory analyses were performed at the hospital's central, certified laboratory. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation. UACR was calculated in mg/g.

Study Endpoints

The primary endpoints were:

1. The mean annual rate of eGFR decline (mL/min/1.73m²/year), calculated for each patient using linear regression of all available eGFR measurements over the 5-year period.
2. The absolute change in median UACR from baseline to year 5.

Secondary endpoints included the 5-year incidence of:

1. New-onset macroalbuminuria (UACR >300 mg/g on two consecutive measurements in patients with baseline UACR <300 mg/g).
2. A composite renal outcome, defined as a sustained eGFR decline of >40% from baseline or progression to ESRD (eGFR <15 mL/min/1.73m² or initiation of dialysis).

Statistical Analysis: Data were analyzed using SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY). Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data or median [interquartile range, IQR] for skewed data.

Categorical variables were presented as counts and percentages (%). Baseline characteristics between the two groups were compared using an independent samples t-test or Mann-Whitney U test

for continuous variables and the Chi-square test for categorical variables.

The primary outcome of annual eGFR decline was compared using an independent samples t-test. Changes in UACR were compared using the Mann-Whitney U test. The incidence of secondary endpoints was compared using the Chi-square test. A p-value of <0.05 was considered statistically significant.

Results

Baseline Characteristics: A total of 250 patients (120 in the uncontrolled group, 130 in the controlled group) completed the 5-year follow-up. The baseline demographic and clinical characteristics of the study cohort are presented in Table 1. The two groups were well-matched with respect to age, sex distribution, duration of diabetes, and baseline eGFR. As per the study design, the mean HbA1c was significantly higher in the uncontrolled group (9.4 ± 0.8%) compared to the controlled group (6.7 ± 0.4%; p<0.001).

While systolic blood pressure and BMI were slightly higher in the uncontrolled group, these differences were not statistically significant. The use of RAAS inhibitors was high and comparable between groups.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Cohort

Characteristic	Uncontrolled Group (n=120)	Controlled Group (n=130)	p-value
Age (years)	61.2 ± 8.5	60.5 ± 9.1	0.582
Male Sex, n (%)	68 (56.7)	70 (53.8)	0.651
Duration of Diabetes (years)	14.5 ± 5.2	13.9 ± 6.0	0.467
HbA1c (%)	9.4 ± 0.8	6.7 ± 0.4	<0.001
BMI (kg/m²)	31.8 ± 4.6	30.9 ± 5.1	0.189
Systolic Blood Pressure (mmHg)	134 ± 12	131 ± 11	0.065
Diastolic Blood Pressure (mmHg)	81 ± 8	80 ± 7	0.314
eGFR (mL/min/1.73m²)	84.5 ± 15.2	86.1 ± 14.8	0.455
UACR (mg/g), median [IQR]	25 [15–40]	22 [14–35]	0.203
Use of RAAS inhibitors, n (%)	102 (85.0)	113 (86.9)	0.678
Current Smoker, n (%)	19 (15.8)	18 (13.8)	0.662
Data are mean ± SD, n (%), or median [IQR].			

Primary Outcomes: Changes in Renal Function: Over the 5-year follow-up period, patients in the uncontrolled group experienced a significantly more rapid decline in renal function. The mean annual eGFR decline in the uncontrolled group was -4.8 ± 1.2 mL/min/1.73m², which was three times greater than the decline of -1.6 ± 0.8 mL/min/1.73m² observed in the controlled group (p<0.001). Similarly, albuminuria progression was markedly more pronounced in the uncontrolled cohort.

The median UACR in the uncontrolled group increased from 25 mg/g to 88 mg/g, whereas in the controlled group it showed only a modest increase from 22 mg/g to 31 mg/g. The difference in the changeover 5 years was highly statistically significant (p<0.001). These findings are summarized in Table 2.

Table 2. Changes in Renal Function Parameters Over 5 Years

Parameter	Uncontrolled Group (n=120)	Controlled Group (n=130)	p-value
eGFR (mL/min/1.73m²)			
Baseline	84.5 ± 15.2	86.1 ± 14.8	0.455
Year 5	60.5 ± 14.1	78.1 ± 13.9	<0.001
Mean Annual Decline	-4.8 ± 1.2	-1.6 ± 0.8	<0.001
UACR (mg/g), median [IQR]			
Baseline	25 [15–40]	22 [14–35]	0.203
Year 5	88 [45–155]	31 [20–48]	<0.001
Median Change (Year 5 - Baseline)	+63	+9	<0.001

Secondary Outcomes: Incidence of Clinical Renal Endpoints: The incidence of adverse clinical renal endpoints at 5 years was significantly higher in the uncontrolled group (Table 3). New-onset macroalbuminuria developed in 28.3% (34/120) of patients in the uncontrolled group, compared to only 5.4% (7/130) in the controlled group (p<0.001). The composite renal endpoint (sustained >40% eGFR decline or ESRD) occurred in 31.7% (38/120) of patients with uncontrolled

diabetes, in stark contrast to just 6.2% (8/130) of those with controlled diabetes (p<0.001).

Table 3. Incidence of Clinical Renal Endpoints at 5 Years

Endpoint	Uncontrolled Group (n=120)	Controlled Group (n=130)	p-value
New-Onset Macroalbuminuria, n (%)	34 (28.3)	7 (5.4)	<0.001
>40% Sustained eGFR Decline, n (%)	35 (29.2)	8 (6.2)	<0.001
Composite Renal Endpoint, n (%)*	38 (31.7)	8 (6.2)	<0.001

Discussion

This 5-year prospective cohort study provides compelling evidence that persistent poor glycemic control in patients with T2DM is a powerful driver of diabetic nephropathy progression. Our principal finding—a three-fold faster rate of eGFR decline in patients with HbA1c >8.5% compared to those with HbA1c <7.0%—quantifies the substantial renal risk associated with sustained hyperglycemia in a real-world clinical setting. These results not only confirm but also extend the findings of landmark clinical trials by demonstrating the magnitude of this effect over a multi-year period in a contemporary patient population.

The observed annual eGFR decline of 4.8 mL/min/1.73m² in our uncontrolled cohort is alarming, as it far exceeds the expected age-related decline of approximately 1 mL/min/1.73m²/year and places these patients on an accelerated trajectory toward ESRD. This rate is consistent with findings from post-hoc analyses of major trials. For instance, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial showed that each 1% increase in HbA1c was associated with a higher risk of developing new or worsening nephropathy [9]. Our data provide a clear longitudinal picture of this association, demonstrating a stark divergence in renal function trajectories based on glycemic control status. The minimal eGFR decline in our controlled group (-1.6 mL/min/1.73m²/year) highlights the profound kidney-protective effect of achieving and maintaining glycemic targets.

The parallel progression of albuminuria in our uncontrolled cohort further reinforces the central role of hyperglycemia in driving glomerular injury. The significant increase in UACR, leading to a high incidence of new-onset macroalbuminuria (28.3%), is a direct clinical manifestation of the underlying pathophysiological processes, including glomerular hyperfiltration, endothelial damage, and podocyte injury, which are all exacerbated by high glucose levels [4, 5]. This finding is clinically significant, as albuminuria is not merely a marker of kidney damage but also an independent risk factor for both CKD progression and cardiovascular events [10].

The mechanisms linking chronic hyperglycemia to accelerated renal decline are well-documented. Hyperglycemia-induced overproduction of reactive oxygen species, accumulation of AGEs, and aberrant activation of intracellular signaling pathways contribute to renal inflammation and fibrosis, the final common pathways of kidney damage [11-13]. While modern therapies such as RAAS inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists have revolutionized the management of DN, our study underscores that their benefits are maximized in the context of good glycemic control. Indeed, while RAAS inhibitor use was high in both our groups, it was insufficient to halt progression in the face of severe, persistent hyperglycemia. This suggests that glycemic control remains a non-negotiable, foundational element of renal protection in T2DM [14,15].

This study has several strengths, including its prospective design, a 5-year follow-up period, the use of standardized laboratory measurements, and the focus on well-defined, clinically relevant patient groups. However, some limitations must be acknowledged. First, as an observational study, we can demonstrate strong associations but cannot definitively prove causality. Unmeasured confounding variables may have influenced the outcomes. Second, the study was conducted at a single tertiary care center, which may limit the generalizability of our findings to other populations or healthcare settings. Finally, we did not systematically collect data on the use of newer cardiorenal protective agents like SGLT2 inhibitors, which became more widespread towards the end of our study period and could influence DN progression.

Conclusion

In conclusion, this 5-year prospective study demonstrates that patients with T2DM and persistent poor glycemic control experience a dramatically accelerated progression of diabetic nephropathy, characterized by a three-fold faster decline in eGFR and a marked increase in albuminuria compared to patients with sustained good glycemic control. The incidence of clinically significant adverse renal events was more than five times higher in the uncontrolled group. These findings provide a stark, quantitative reminder of the critical importance of achieving and

maintaining long-term glycemic targets as a cornerstone strategy to preserve renal function and prevent the devastating consequences of diabetic kidney disease.

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