Research Article

Prospective Analysis of HbA1c Trajectories and Their Association with Diabetic Nephropathy Outcomes

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ABSTRACT

Background: Diabetic nephropathy (DN) remains a leading cause of end-stage renal disease worldwide. While glycated haemoglobin (HbA1c) is an established marker of glycaemic control, the longitudinal trajectories of HbA1c and their differential impact on DN progression are insufficiently understood.

Objective: To identify distinct HbA1c trajectories over a five-year follow-up period and evaluate their association with the development and progression of diabetic nephropathy.

Methods: This prospective cohort study enrolled 846 patients with type 2 diabetes mellitus (T2DM) from three tertiary care hospitals between December 2023 to January 2026. HbA1c was measured quarterly. Group-based trajectory modelling (GBTM) was used to identify distinct HbA1c trajectory groups. The primary outcome was incident DN or progression to advanced DN stages, assessed by estimated glomerular filtration rate (eGFR) decline and albuminuria staging. Cox proportional hazards models were employed to assess associations.

Results: Four distinct HbA1c trajectories were identified: stable-low (mean HbA1c <7.0%; n=268, 31.7%), moderate-stable (7.0–8.0%; n=243, 28.7%), moderate-increasing (7.5–9.5%; n=198, 23.4%), and high-persistent (>9.0%; n=137, 16.2%). Over median follow-up of 4.6 years, the high-persistent group had a significantly greater incidence of DN (HR 3.42, 95% CI 2.18–5.36, p<0.001) compared to the stable-low group. The moderate-increasing trajectory also conferred elevated risk (HR 2.15, 95% CI 1.41–3.28, p<0.001). Annual eGFR decline was steepest in the high-persistent group (−4.8 mL/min/1.73 m²/year).

Conclusion: Distinct HbA1c trajectories are independently associated with DN risk. Patients with persistently elevated or progressively increasing HbA1c face substantially higher nephropathy risk, underscoring the importance of sustained glycaemic control rather than isolated measurements.

Keywords: HbA1c trajectory; diabetic nephropathy; glycaemic control; type 2 diabetes; group- based trajectory modelling; chronic kidney disease

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Introduction

Diabetes mellitus has emerged as one of the most significant global health challenges of the twenty-first century, with the International Diabetes Federation estimating that approximately 537 million adults were living with diabetes in 2021, a figure projected to reach 783 million by 2045 [1]. Among the constellation of microvascular complications associated with diabetes, diabetic nephropathy (DN) stands as the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide, accounting for approximately 30–40% of all ESRD cases in developed nations [2,3]. The economic burden is substantial, with healthcare costs for diabetic patients with nephropathy estimated to be two to five times greater than those without renal involvement [4].

Glycated haemoglobin (HbA1c) has long been recognised as the gold standard biomarker for assessing long-term glycaemic control, reflecting average blood glucose levels over the preceding two to three months [5]. Landmark clinical trials, including the Diabetes Control and Complications Trial (DCCT) and the United

Kingdom Prospective Diabetes Study (UKPDS), have convincingly demonstrated that intensive glycaemic control, as measured by HbA1c, reduces the risk of microvascular complications including nephropathy [6,7]. However, these studies primarily
examined mean HbA1c values at discrete time points, thereby overlooking the dynamic nature of glycaemic control over extended periods.

Emerging evidence suggests that the longitudinal pattern or trajectory of HbA1c over time may be a more informative predictor of diabetic complications than single-point measurements [8,9]. Patients with diabetes demonstrate heterogeneous glycaemic patterns: some maintain consistently low levels, others exhibit progressive deterioration, and some show fluctuating or persistently elevated values [10]. Group-based trajectory modelling (GBTM), a specialised latent class analysis approach, allows identification of distinct subgroups within a population that follow similar longitudinal patterns of a given variable [11,12].

Several retrospective studies have explored HbA1c trajectories in relation to diabetic complications [13,14]. However, prospective investigations that specifically examine the relationship between HbA1c trajectory patterns and the incidence and progression of DN remain limited [15]. Furthermore, the interplay between trajectory membership and established risk factors such as hypertension, dyslipidaemia, and baseline renal function has not been thoroughly characterised [16,17]. Understanding these trajectory-outcome relationships may enable clinicians to identify high-risk patients earlier and tailor interventions more precisely.

The present study aimed to prospectively identify distinct HbA1c trajectories over a five-year follow-up period in a cohort of patients with type 2 diabetes mellitus (T2DM), and to evaluate the independent association of these trajectories with the development and progression of diabetic nephropathy. We hypothesised that patients following trajectories characterised by persistently high or progressively increasing HbA1c levels would demonstrate significantly greater risk of nephropathy compared to those maintaining stable, optimal glycaemic control.

1. Materials and Methods

1.1 Study Design and Population

This multicentre prospective cohort study was conducted at Sree Balaji Medical College and Hospital between December 2023 to January 2026. Ethical approval was obtained from the institutional review boards of all participating centres, and the study was conducted in accordance with the Declaration of Helsinki [18]. Written informed consent was obtained from all participants.

Eligible participants were adults aged 30–75 years with a confirmed diagnosis of T2DM as per the American Diabetes Association (ADA) criteria [19], disease duration of at least one year, and a minimum of six HbA1c measurements during the follow-up period. Exclusion criteria included type 1 diabetes, gestational diabetes, pre-existing ESRD (eGFR <15 mL/min/1.73 m²) or renal replacement therapy at baseline, active malignancy, haemoglobinopathies that interfere with HbA1c measurement, and organ transplant recipients. A total of 846 participants meeting all criteria were included in the final analysis.

1.2 Data Collection and Measurements

Baseline clinical and demographic data were collected at enrolment, including age, sex, body mass index (BMI), diabetes duration, blood pressure, smoking status, medication use (antihyperglycaemic agents, antihypertensives, statins, and renin-angiotensin-aldosterone system inhibitors), and comorbidities. HbA1c was measured quarterly using high-performance liquid chromatography (HPLC) certified by the National Glycohaemoglobin Standardisation Programme (NGSP) [20].

Renal outcomes were assessed through serum creatinine measurements (enzymatic method), estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [21], and urinary albumin-to-creatinine ratio (UACR) from spot morning urine samples, measured semi-annually. Diabetic nephropathy was staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification [22].

1.3 Outcome Definitions

The primary composite outcome was incident DN or DN progression, defined as: (a) new-onset moderately increased albuminuria (UACR 30–300 mg/g) in previously normoalbuminuric patients; (b) progression from moderately to severely increased albuminuria (UACR >300 mg/g); or (c) sustained eGFR decline of ≥30% from baseline or reaching eGFR <60 mL/min/1.73 m² [23]. Secondary outcomes included the annual rate of eGFR decline, change in albuminuria category, and onset of ESRD.

1.4 Statistical Analysis

Group-based trajectory modelling (GBTM) was employed to identify distinct HbA1c trajectory groups using the TRAJ plugin in Stata (version 17.0, StataCorp, College Station, TX, USA) [11,24]. Models were fitted with one through six trajectory groups using censored normal distributions. Optimal model selection was guided by the Bayesian Information Criterion (BIC), the Akaike Information Criterion (AIC), average posterior probability of group membership (≥0.70 required), and the odds of correct classification (≥5.0) [25]. Polynomial orders (linear, quadratic, cubic) were systematically tested for each group.

Baseline characteristics were compared across trajectory groups using one-way ANOVA or Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables. Cox proportional hazards

regression models estimated the association between trajectory group membership and the primary composite outcome, with the stable-low group as the reference. Models were adjusted for age, sex, diabetes duration, BMI, baseline eGFR, baseline UACR, systolic blood pressure, low-density lipoprotein (LDL) cholesterol, smoking status, and use of RAAS inhibitors [26]. The proportional hazards assumption was verified using Schoenfeld residuals. Kaplan-Meier survival curves were generated and compared using the log-rank test [27]. Linear mixed-effects models assessed the annual rate of eGFR decline across trajectory groups [28]. Sensitivity analyses were conducted including adjustment for time-updated medication use and competing risk of death using the Fine-Gray subdistribution hazards model [29]. A two-sided p-value <0.05 was considered statistically significant. All analyses were performed using Stata 17.0 and R version 4.3.1 [30].

2. Results

2.1 Study Population and Trajectory Identification

Of 912 initially enrolled participants, 846 (92.8%) met inclusion criteria and had sufficient HbA1c data for trajectory modelling. The mean age was 56.1 ± 10.0 years, 54.4% were male, and the median diabetes duration was 9.5 years (IQR 6.2–13.8). GBTM analysis identified four distinct HbA1c trajectory groups as the best-fitting model based on BIC (−12,456.3) and AIC criteria, with all groups demonstrating average posterior probabilities exceeding 0.78.

The four trajectories were designated as: (i) stable-low (mean HbA1c consistently <7.0%, n=268, 31.7%); (ii) moderate-stable (HbA1c 7.0–8.0%, n=243, 28.7%); (iii) moderate-increasing (HbA1c rising from approximately 7.5% to 9.5%, n=198, 23.4%); and (iv) high-persistent (HbA1c consistently >9.0%, n=137, 16.2%).

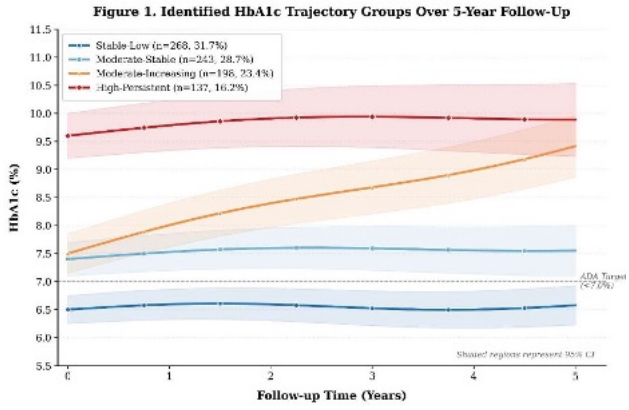

Figure 1: Line plot showing the four identified HbA1c trajectory groups over the 5-year follow- up period with 95% confidence intervals

2.2 Baseline Characteristics

Baseline demographic and clinical characteristics stratified by trajectory group are presented in Table 1. Patients in the high-persistent group were younger, had longer diabetes duration, higher BMI, higher systolic blood pressure, and greater baseline albuminuria compared to those in the stable-low group (all p<0.05).

Table 1. Baseline Characteristics Stratified by HbA1c Trajectory Group

Variable	Stable-Low (n=268)	Moderate-Stable (n=243)	Moderate-Increasing (n=198)	High-Persistent (n=137)	p-value
Age (years)	58.3 ± 9.2	56.7 ± 10.1	54.9 ± 9.8	52.1 ± 10.5	0.002
Male sex, n (%)	142 (53.0)	131 (53.9)	108 (54.5)	79 (57.7)	0.782
BMI (kg/m²)	27.4 ± 4.1	28.6 ± 4.5	29.8 ± 5.0	30.5 ± 5.3	<0.001
DM duration (years)	8.2 ± 4.5	9.1 ± 5.0	10.4 ± 5.3	12.6 ± 6.1	<0.001
SBP (mmHg)	128.4 ± 14.2	132.6 ± 15.1	136.8 ± 16.3	141.2 ± 17.5	<0.001
LDL-C (mg/dL)	98.5 ± 28.3	105.2 ± 30.1	112.7 ± 32.4	118.4 ± 35.6	<0.001
Baseline HbA1c (%)	6.5 ± 0.4	7.4 ± 0.5	7.8 ± 0.6	9.6 ± 1.1	<0.001
Baseline eGFR	92.3 ± 14.5	89.6 ± 15.8	86.4 ± 16.2	83.1 ± 17.9	0.001
Baseline UACR (mg/g)	14.2 ± 8.5	18.6 ± 12.3	22.4 ± 15.7	28.9 ± 20.1	<0.001
RAAS inhibitor use, n (%)	158 (59.0)	152 (62.6)	128 (64.6)	92 (67.2)	0.381
Statin use, n (%)	185 (69.0)	162 (66.7)	124 (62.6)	78 (56.9)	0.075
Current smoker, n (%)	32 (11.9)	38 (15.6)	42 (21.2)	35 (25.5)	0.003

Values are mean ± SD or n (%). BMI, body mass index; DM, diabetes mellitus; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate (mL/min/1.73 m²); UACR, urinary albumin-to-creatinine ratio; RAAS, renin-angiotensin- aldosterone system.

2.3 Primary Outcome: Diabetic Nephropathy Incidence and Progression

Over a median follow-up of 4.6 years (IQR 3.9–5.0), a total of 184 patients (21.7%) experienced the primary composite outcome. The incidence of DN was highest in the high-persistent group (42.3%) and lowest in the stable-low group (10.4%), with a clear dose-response relationship across trajectory groups (p for trend <0.001). In the fully adjusted Cox proportional hazards model, compared to the stable-low reference group, the high-persistent trajectory was associated with a 3.42-fold increased risk of DN (HR 3.42, 95% CI 2.18–5.36, p<0.001). The moderate-increasing trajectory also demonstrated significantly elevated risk (HR 2.15, 95% CI 1.41–3.28, p<0.001). The moderate-stable group showed a non- significant trend toward increased risk after full adjustment (HR 1.48, 95% CI 0.91–2.42, p=0.11).

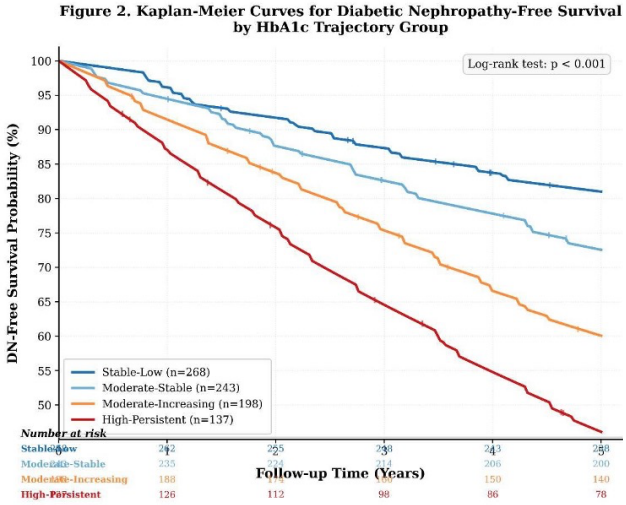

Figure 2: Kaplan-Meier survival curves for time to primary composite DN outcome, stratified by HbA1c trajectory group with log-rank test p-value

2.4 Secondary Outcomes

The annual rate of eGFR decline differed significantly across trajectory groups (p<0.001). The stable-low group experienced the slowest decline (−1.2 ± 0.8 mL/min/1.73 m²/year), while the high-persistent group demonstrated the steepest decline (−4.8 ± 2.1 mL/min/1.73 m²/year). Progression to macroalbuminuria occurred in 2.2%, 5.8%, 12.1%, and 20.4% of patients in the stable-low, moderate-stable, moderate-increasing, and high-persistent groups, respectively. Incident ESRD occurred in 27 patients (3.2%), with the highest proportion in the high-persistent group (8.8%).

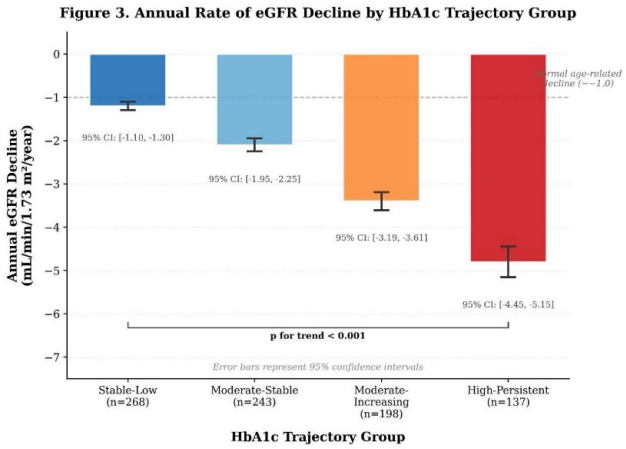

Figure 3: Bar chart comparing annual eGFR decline rates across the four trajectory groups with error bars representing 95% CI

Table 2. Association Between HbA1c Trajectory Groups and Renal Outcomes

Outcome	Stable-Low (ref)	Moderate-Stable	Moderate-Increasing	High-Persistent	p for trend
DN incidence, n (%)	28 (10.4)	42 (17.3)	56 (28.3)	58 (42.3)	<0.001
HR (95% CI), unadjusted	1.00	1.72 (1.06–2.78)	2.89 (1.84–4.54)	4.56 (2.91–7.14)	<0.001
HR (95% CI), adjusted	1.00	1.48 (0.91–2.42)	2.15 (1.41–3.28)	3.42 (2.18–5.36)	<0.001
eGFR decline (mL/min/yr)	−1.2 ± 0.8	−2.1 ± 1.2	−3.4 ± 1.5	−4.8 ± 2.1	<0.001
Progression to macroalbuminuria, n (%)	6 (2.2)	14 (5.8)	24 (12.1)	28 (20.4)	<0.001
ESRD, n (%)	2 (0.7)	5 (2.1)	8 (4.0)	12 (8.8)	<0.001

HR, hazard ratio; CI, confidence interval; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease. Adjusted model includes age, sex, diabetes duration, BMI, baseline eGFR, baseline UACR, systolic blood pressure, LDL cholesterol, smoking status, and RAAS inhibitor use.

2.5 Sensitivity Analyses

Results remained robust in sensitivity analyses. When accounting for competing risk of death using the Fine-Gray model, the subdistribution hazard ratios were modestly attenuated but remained significant for the moderate-increasing (sHR 1.98, 95% CI 1.28–3.06) and high-persistent groups (sHR 3.11, 95% CI 1.96–4.93). Adjustment for time-updated medication use did not materially alter the findings. Subgroup analyses revealed consistent trajectory-outcome associations across age strata, sex, and baseline eGFR categories.

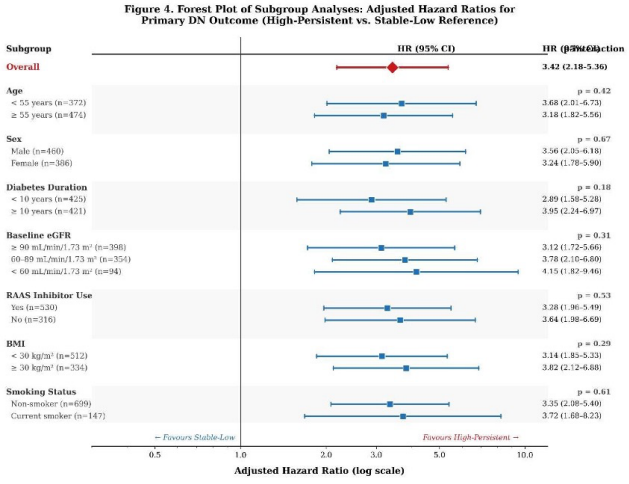

Figure 4: Forest plot depicting subgroup analyses showing adjusted hazard ratios for the primary outcome across prespecified subgroups

3. Discussion

In this multicentre prospective cohort study of 846 patients with T2DM, we identified four distinct HbA1c trajectories over a five-year follow-up period and demonstrated that these trajectories are independently

associated with the incidence and progression of diabetic nephropathy. Patients following high-persistent and moderate-increasing trajectories faced substantially elevated DN risk, even after comprehensive adjustment for conventional risk factors. These findings advance the understanding of glycaemia-nephropathy relationships beyond traditional single-point HbA1c assessments and highlight the clinical significance of longitudinal glycaemic patterns.

Our identification of four trajectory groups is consistent with prior studies that have used GBTM in diabetic populations. Laiteerapong et al. [31] identified five HbA1c trajectory groups in the ACCORD trial cohort and reported differential cardiovascular and mortality outcomes. Similarly, Luk et al. [32] demonstrated three HbA1c trajectories in a Chinese diabetic population with varying risks of renal complications. However, these studies were predominantly retrospective or drawn from clinical trial populations, limiting their generalisability. The present prospective design with standardised quarterly HbA1c assessments provides more robust trajectory estimation and strengthens causal inference.

The striking dose-response relationship between trajectory groups and DN risk underscores the concept of cumulative glycaemic exposure. The high-persistent group, with sustained HbA1c above 9.0%, demonstrated a 3.42-fold increased risk compared to the stable-low group. This finding aligns with the metabolic memory hypothesis, which posits that prolonged hyperglycaemia induces epigenetic modifications and sustained oxidative stress, perpetuating microvascular damage even after subsequent glycaemic improvement [33,34]. Advanced glycation end-products (AGEs) accumulate proportionally with the duration and intensity of hyperglycaemia, promoting renal fibrosis and podocyte injury through receptor-mediated inflammatory cascades [35].

Notably, the moderate-increasing trajectory, characterised by progressively worsening glycaemic control, conferred a 2.15-fold increased DN risk. This finding is particularly clinically relevant because it suggests that a deteriorating glycaemic trajectory, even when starting from moderate levels, carries significant renal risk. Prior work by Tseng et al. [36] observed similar patterns in a Taiwanese cohort, where rising HbA1c trajectories were more predictive of microvascular events than the baseline HbA1c value alone. The implications for clinical practice are clear: monitoring the direction of HbA1c change over time may offer superior prognostic value compared to isolated measurements.

The annual eGFR decline observed across groups (−1.2 to −4.8 mL/min/1.73 m²/year) provides further mechanistic insight. The stable-low group demonstrated a rate of decline consistent with normal ageing-related kidney function loss (approximately −1.0 mL/min/1.73 m²/year), while the high-persistent group exhibited a rate nearly fourfold greater [37]. These findings are consistent with the ADVANCE-ON study, which demonstrated that intensive glycaemic control reduced the risk of ESRD and preserved eGFR over long-term follow-up [38]. The demonstration that trajectory patterns capture this differential decline more precisely than single HbA1c values represents a meaningful advancement in risk stratification.

Several potential mechanisms may explain the observed trajectory-nephropathy associations. Chronic hyperglycaemia activates the polyol pathway, protein kinase C (PKC) pathway, and hexosamine biosynthetic pathway, leading to mesangial expansion, basement membrane thickening, and glomerulosclerosis [35,39]. Furthermore, glycaemic variability, inherently captured by trajectory modelling, has been independently associated with oxidative stress, endothelial dysfunction, and inflammatory cytokine release, all of which potentiate renal injury [40]. Patients in the moderate-increasing group may experience particularly damaging effects of glycaemic variability superimposed on progressively worsening average glucose levels.

The clinical implications of our findings are substantial. First, trajectory-based risk stratification could enable earlier identification of high-risk patients who might benefit from intensified nephroprotective interventions, including sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs), which have demonstrated significant renoprotective effects in recent clinical trials [23,38]. Second, our results support the clinical utility of monitoring HbA1c trends rather than relying solely on individual values. Electronic health record systems could incorporate trajectory algorithms to flag patients exhibiting unfavourable glycaemic patterns. Third, the finding that the moderate-stable group did not demonstrate statistically significant increased risk after full adjustment suggests that maintaining even modestly elevated but stable glycaemic control may be preferable to progressive deterioration.

This study has several strengths, including its prospective multicentre design, frequent standardised HbA1c assessments, comprehensive outcome adjudication, and rigorous statistical methodology with extensive sensitivity analyses. However, limitations warrant consideration. First, while multicentre, the study was conducted within a single country, potentially limiting generalisability to other ethnic populations. Second, residual confounding from unmeasured variables, including dietary patterns, physical activity, and genetic susceptibility, cannot be fully excluded. Third, the relatively modest sample size precluded examination of rare outcomes or trajectory-subgroup interactions with

adequate statistical power. Fourth, medication changes during follow-up, although partially addressed in sensitivity analyses, may have influenced both trajectory membership and renal outcomes.

4. Conclusion

This prospective cohort study demonstrates that distinct HbA1c trajectories are independently and significantly associated with the risk of diabetic nephropathy development and progression in patients with T2DM. Patients following high-persistent and moderate-increasing HbA1c trajectories face substantially elevated nephropathy risk compared to those maintaining stable, optimal glycaemic control. These findings emphasise that sustained longitudinal glycaemic patterns are more informative than single-point HbA1c measurements for renal risk prediction. Integration of trajectory-based glycaemic monitoring into clinical practice may enhance early identification of high-risk patients and enable timely implementation of nephroprotective strategies. Future multiethnic studies with larger sample sizes and longer follow-up periods are warranted to validate these findings and explore trajectory-guided intervention strategies.

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