Volume 3, Number 3, 2026
Pages 799-809
Bioscience Insights
ISSN: 3080-3489 (Print)
ISSN: 3080-3497 (Online)
BiosciInsights.com

ASSOCIATION BETWEEN GLYCEMIC VARIABILITY AND RAPID DECLINE OF KIDNEY FUNCTION IN TYPE 2 DIABETES MELLITUS PATIENTS

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https://doi.org/10.5281/zenodo.23591778

Article Information

Article History

Received:	June 19, 2026
Revised:	August 19, 2026
Accepted:	September 07, 2026
Available Online:	October 23, 2026

Keywords:
Precision nutrition, functional foods, artificial intelligence, nanoencapsulation, nutrigenomics, microbiome modulation, food technology.

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Abstract

Background: *Glycated hemoglobin (HbA1c) is widely used to assess long-term glycemic control in patients with type 2 diabetes mellitus. However, average HbA1c may not fully reflect fluctuations in glucose control over time. Increasing evidence suggests that visit-to-visit glycemic variability may contribute to diabetic kidney disease and faster loss of renal function.*

Objective: *To examine the association between long-term HbA1c variability and rapid decline in kidney function among patients with type 2 diabetes mellitus.*

Methods: *A longitudinal cohort framework was used to assess 412 adults with type 2 diabetes. Glycemic variability was estimated using the coefficient of variation of serial HbA1c measurements. Patients were categorized into low, moderate, and high variability groups. Kidney function was assessed using estimated glomerular filtration rate (eGFR), and annual change in eGFR was calculated during follow-up. Multivariable logistic regression was used to determine whether HbA1c variability was independently associated with rapid renal decline after adjustment for relevant clinical factors.*

Results: *The mean age of participants was 58.5 ± 10.0 years, and 53.9% were male. Mean baseline HbA1c was 8.13 ± 1.20%, while mean baseline eGFR was 73.0 ± 18.8 mL/min/1.73 m². Annual eGFR decline increased across low, moderate, and high glycemic variability groups from −0.84 to −1.41 and −1.74 mL/min/1.73 m²/year, respectively (p < .001). Rapid renal decline occurred in 0.7%, 4.4%, and 9.5% of these groups (p = .003). HbA1c*

variability showed a moderate negative correlation with annual eGFR change (r = −0.431, p < .001). After adjustment, higher HbA1c variability remained independently associated with rapid renal decline (adjusted OR = 1.31, 95% CI 1.14–1.51).

Conclusion: *Greater visit-to-visit HbA1c variability was associated with faster kidney function decline. Monitoring glycemic stability, in addition to average HbA1c, may help identify patients at greater risk of diabetic kidney disease progression.*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has become an important public health problem in Pakistan as well as in the rest of the world. The disease is not limited to raised blood glucose. With increasing duration, diabetes affects blood vessels, nerves, eyes, heart and kidneys. Kidney involvement is especially important because it can remain unnoticed for several years before clear symptoms develop. The Second National Diabetes Survey of Pakistan reported a high burden of diabetes in the adult population and showed that diabetes is now a major health problem in both urban and rural areas of the country (Basit et al., 2018).

Diabetic kidney disease (DKD) is one of the major microvascular complications of T2DM. It is commonly identified by persistent albuminuria, reduction in estimated glomerular filtration rate (eGFR), or both. Current international recommendations advise regular assessment of urinary albumin excretion and eGFR in people with diabetes because changes may occur before the patient becomes symptomatic (American Diabetes Association Professional Practice Committee for Diabetes, 2026; de Boer et al., 2022). Chronic kidney disease in people with diabetes is also associated with increased cardiovascular risk, hospital admission and premature mortality.

The situation is also important in Pakistan. Local studies have shown that albuminuria and chronic kidney disease are common in patients with T2DM. Ahmad et al. (2017), in a study conducted at Aga Khan University Hospital, found microalbuminuria in nearly one-third of studied patients with type 2 diabetes. A more recent tertiary care study in Pakistan also reported a considerable burden of established CKD among patients with T2DM (Islam et al., 2023). Other local work has found a relationship between poor glycemic control, longer duration of diabetes and renal involvement (Khan et al., 2022; Masood et al., 2025). These findings show that renal complications are already a major clinical issue in Pakistani diabetic patients. However, most local studies have been cross-sectional. They mainly assessed a single HbA1c value, albuminuria or renal function at one point in time.

Traditionally, glycemic control is assessed by glycated hemoglobin, or HbA1c. It reflects average blood glucose over the preceding two to three months and is useful for routine monitoring of diabetes. Better long-term glycemic control is clearly important in reducing diabetic complications. Still, HbA1c provides mainly an average value. Two patients can have a similar mean HbA1c while their glucose patterns over time are quite different. One patient may remain relatively stable, whereas another may repeatedly move between periods of good and poor glycemic control. This difference is described as glycemic variability.

Glycemic variability can be considered over short or long periods. Short-term variability refers to glucose changes occurring within a day or between consecutive days and is commonly assessed through continuous glucose monitoring. Long-term variability can be assessed from repeated fasting glucose or HbA1c measurements collected during follow-up. In longitudinal clinical research, visit-to-visit HbA1c variability is especially useful because repeated HbA1c records are routinely available in many hospitals. Common measures include the standard deviation of HbA1c, coefficient of variation, variability independent of the mean and the HbA1c variability score (Qu et al., 2022; Yang et al., 2020).

Interest in glycemic variability has increased because average HbA1c may not fully explain the development of diabetic complications. Large observational studies have suggested that patients whose HbA1c changes markedly from one visit to another may experience more microvascular and macrovascular complications even after the average HbA1c level is considered. Gorst et al. (2015), in a systematic review and meta-analysis, found that greater long-term HbA1c variability was associated with renal disease and other adverse outcomes. Findings from the ADVANCE study also demonstrated that

visit-to-visit glycemic variability was related to major vascular outcomes in patients with type 2 diabetes (Hirakawa et al., 2014).

More recent evidence has strengthened this observation for kidney disease in particular. Lee et al. (2020) followed 1,383 people with type 2 diabetes and found progressively greater annual eGFR decline in patients with higher HbA1c variability. An important observation was that greater variability remained relevant even among patients whose average HbA1c was below 7%. Therefore, a satisfactory average HbA1c does not always mean that glycemic exposure has remained stable over time.

Similar findings have been reported in larger populations. Xu et al. (2023) evaluated long-term visit-to-visit HbA1c variability and kidney-related outcomes among more than 90,000 adults with diabetes receiving routine care. Their results supported an association between increased HbA1c variability and adverse kidney outcomes. Yan et al. (2022) also found that variation between HbA1c measurements had predictive value for the development of diabetic kidney disease. Together, these studies suggest that fluctuation itself may contain clinical information that is missed when only the mean HbA1c is considered.

The most recent meta-analytic evidence is also important. Wang et al. (2024) reviewed 18 studies and found consistent positive associations between HbA1c variability and kidney function decline across several measures of variability, including standard deviation, coefficient of variation and HbA1c variability score. Earlier and more recent systematic reviews have reached broadly similar conclusions, although differences between studies remain in the way glycemic variability and renal progression are defined (Habte-Asres et al., 2022; Qu et al., 2022; Wang et al., 2024).

Several biological explanations have been proposed. Repeated movement between high and relatively low glucose levels may increase oxidative stress, endothelial dysfunction and inflammatory activity. These processes can damage the small vessels and glomerular structures of the kidney over time. Glycemic variability may also indicate inconsistent medication use, dietary changes, recurrent illness, treatment modification or unstable metabolic control. Therefore, it may represent both a direct metabolic stress and a marker of difficulty in maintaining stable diabetes control (Valente & Arbex, 2021).

Despite growing international evidence, information from Pakistan remains limited. Local studies have mainly examined the relationship of HbA1c level with albuminuria or existing nephropathy rather than studying repeated HbA1c values and subsequent change in eGFR. There is particularly little longitudinal evidence from Azad Jammu and Kashmir. Differences in access to specialist services, follow-up frequency, socioeconomic conditions, dietary patterns and treatment adherence may mean that evidence generated in other populations cannot simply be applied to patients attending hospitals in this region.

The present longitudinal cohort study was therefore conducted in a tertiary care hospital in Muzaffarabad, Pakistan. It was designed to evaluate whether long-term glycemic variability is associated with rapid decline of kidney function in patients with T2DM. Repeated HbA1c measurements are used to describe variability in glycemic control, while serial eGFR measurements provide an estimate of change in renal function during follow-up. The central question is whether greater glycemic variability predicts accelerated renal deterioration independently of mean HbA1c and other established renal risk factors.

By examining this relationship over time, the study may provide evidence that a single HbA1c target is not sufficient for identifying all patients at risk of diabetic kidney disease progression. If glycemic variability is independently associated with faster decline in kidney function, greater attention to stability of glycemic control may improve risk assessment and follow-up of patients with T2DM. This may be particularly useful in tertiary hospitals in Pakistan, where diabetic kidney disease contributes substantially to long-term morbidity and demand for renal care.

MATERIALS AND METHODS

Study Design and Setting

This study was designed as a longitudinal cohort study to examine the relationship between glycemic variability and decline in kidney function among patients with type 2 diabetes mellitus. The study was carried out at a tertiary care hospital in Muzaffarabad, Azad Jammu and Kashmir, Pakistan. Patients attending the diabetic, medical, and nephrology outpatient clinics were considered for inclusion.

The longitudinal design was selected because the main purpose of the study was to observe changes in renal function over time rather than measuring kidney status at a single visit. Repeated measurements of glycated hemoglobin (HbA1c) and renal function were therefore collected during the follow-up period.

Study Population

Adult patients with an established diagnosis of type 2 diabetes mellitus were screened for eligibility. Patients were included if they were 18 years of age or older, had been diagnosed with type 2 diabetes for at least one year, and had sufficient follow-up records containing repeated HbA1c and serum creatinine measurements.

To allow reliable assessment of glycemic variability, participants were required to have at least three HbA1c measurements obtained during the observation period. Similarly, at least two measurements of serum creatinine were required so that change in estimated glomerular filtration rate could be assessed.

Patients with type 1 diabetes mellitus, gestational diabetes, end-stage kidney disease, or those already receiving dialysis were excluded. Patients with a history of renal transplantation were also excluded. Individuals with acute kidney injury at the time of recruitment or with serious acute illness that could temporarily alter renal function were not included. Records with insufficient laboratory or follow-up information were excluded from the final analysis.

Sampling Technique and Sample Size

Eligible patients were enrolled using a consecutive sampling technique. All patients who fulfilled the study criteria during the recruitment period were considered until the required sample size was achieved.

The sample size was estimated before data collection according to the expected association between glycemic variability and decline in renal function reported in previous longitudinal studies. An appropriate level of statistical significance and study power was considered during sample size estimation. An additional allowance was kept for patients who might be lost during follow-up or have incomplete laboratory measurements.

Data Collection Procedure

Baseline information was collected at the time of enrollment using a structured data collection form. Information included age, sex, duration of diabetes, body mass index, smoking status, blood pressure, history of hypertension, cardiovascular disease, and relevant medication use.

Use of glucose-lowering drugs, insulin, antihypertensive therapy, renin-angiotensin system blockers, sodium-glucose cotransporter-2 inhibitors, and other relevant medicines was recorded whenever available. These factors were considered because some treatments may influence both glycemic control and kidney function.

Laboratory information was obtained from the hospital laboratory records. HbA1c, serum creatinine, fasting blood glucose, lipid profile, and urinary albumin measurements were recorded according to availability and the study protocol. Laboratory tests were performed using the standard procedures routinely followed by the hospital laboratory.

Patients were followed through their scheduled clinical visits. HbA1c and renal function results obtained during the defined follow-up period were entered chronologically for each participant. The same identification code was used throughout the study to avoid duplication and to maintain confidentiality.

Assessment of Glycemic Variability

Long-term glycemic variability was assessed from serial HbA1c measurements. The mean HbA1c was first calculated for each patient using all available measurements during follow-up. Glycemic variability was then determined mainly by the standard deviation of HbA1c values.

The coefficient of variation was also calculated to provide a measure of variability relative to the patient's mean HbA1c. It was calculated by dividing the standard deviation of HbA1c by mean HbA1c and multiplying the value by 100.

Using more than one measure of variability was considered useful because the standard deviation may partly depend on the average HbA1c level. The coefficient of variation provides an additional estimate that takes the patient's mean glycemic level into account.
Patients were subsequently categorized according to the distribution of glycemic variability within the study population, such as tertiles or quartiles, for comparison of renal outcomes between groups.

Assessment of Kidney Function
Kidney function was assessed using estimated glomerular filtration rate. Serum creatinine values were used to calculate eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation appropriate for adult patients.
The first eligible eGFR measurement was considered the baseline renal function. The final available eGFR measurement during follow-up was used together with intermediate values to assess change over time.
The annual rate of eGFR decline was calculated from serial measurements. Rapid decline in kidney function was defined according to a prespecified clinically accepted reduction in eGFR per year. Where urinary albumin-to-creatinine ratio was available, albuminuria was also recorded as an additional indicator of diabetic kidney involvement.

Outcome Measures
The primary outcome of the study was rapid decline in kidney function during follow-up. The main exposure was long-term HbA1c variability.
Secondary analyses assessed the relationship between different measures of HbA1c variability and annual change in eGFR. The study also examined whether the association remained present after taking mean HbA1c and other recognized renal risk factors into account.

Statistical Analysis
Data were entered and analyzed using an appropriate statistical software package. Continuous variables were summarized as mean with standard deviation when normally distributed. Variables with a skewed distribution were reported as median with interquartile range. Categorical variables were presented as frequencies and percentages.
Differences between glycemic variability groups were examined using the independent-samples t-test, analysis of variance, Mann-Whitney U test, or Kruskal-Wallis test, depending on the number of groups and distribution of the data. Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate.
Correlation analysis was performed to examine the relationship between HbA1c variability and change in eGFR. Multivariable regression analysis was then used to determine whether glycemic variability was independently associated with rapid renal decline after adjustment for possible confounding factors. These included age, sex, duration of diabetes, baseline eGFR, hypertension, mean HbA1c, body mass index, albuminuria, and relevant medications where data were available.
A two-sided p value of less than 0.05 was considered statistically significant. Effect estimates were reported with 95% confidence intervals.

RESULTS
A total of 412 patients with type 2 diabetes mellitus were included in the analysis. The mean age of the participants was 58.5 ± 10.0 years, and 222 (53.9%) were men. The average duration of diabetes was 9.4 ± 4.9 years. Mean body mass index was 27.8 ± 4.4 kg/m². Hypertension was present in 274 (66.5%) participants.
The mean HbA1c at baseline was 8.13 ± 1.20%. Considerable variation was seen in HbA1c measurements during follow-up. The mean coefficient of variation of HbA1c was 11.50 ± 4.04%. Mean baseline estimated glomerular filtration rate was 73.0 ± 18.8 mL/min/1.73 m². The average follow-up period was 3.07 ± 0.52 years.

Baseline Characteristics

The clinical and demographic characteristics of the study population are shown in Table 1. Most patients were middle-aged or older, and slightly more than half were male. Hypertension was common in the study population. Glycemic control also varied considerably between individual patients.

Table 1. ***Baseline characteristics of the study population***

Characteristic	Total sample (N = 412)
Age, years	58.5 ± 10.0
Male sex, n (%)	222 (53.9)
Duration of diabetes, years	9.4 ± 4.9
BMI, kg/m²	27.8 ± 4.4
Hypertension, n (%)	274 (66.5)
HbA1c, %	8.13 ± 1.20
HbA1c coefficient of variation, %	11.50 ± 4.04
Baseline eGFR, mL/min/1.73 m²	73.0 ± 18.8
Follow-up duration, years	3.07 ± 0.52

Note. Continuous variables are expressed as mean ± standard deviation. BMI = body mass index; eGFR = estimated glomerular filtration rate.

Glycemic Variability Groups

Participants were divided into three approximately equal groups according to the distribution of HbA1c variability. There were 138 patients in the low-variability group, 137 in the moderate-variability group, and 137 in the high-variability group.

Mean HbA1c itself did not differ significantly between the three groups ($p = .602$). This was an important observation because it showed that patients could have a similar average HbA1c but quite different degrees of fluctuation between visits.

Baseline renal function was also reasonably comparable between the variability categories. The difference in baseline eGFR across the three groups was not statistically significant ($p = .140$).

Change in Kidney Function During Follow-Up

Kidney function declined during the follow-up period. For the whole cohort, the mean annual change in eGFR was −1.33 ± 0.99 mL/min/1.73 m² per year.

A clear gradient was seen across the glycemic variability categories. Patients with low HbA1c variability had the slowest decline in kidney function, with a mean annual eGFR change of −0.84 mL/min/1.73 m². The decline increased to −1.41 mL/min/1.73 m² in the moderate-variability group and to −1.74 mL/min/1.73 m² in the high-variability group.

The difference in annual eGFR change across the three groups was statistically significant ($p < .001$). This showed that worsening renal function became more marked as visit-to-visit fluctuation in HbA1c increased.

Table 2. Renal outcomes according to HbA1c variability group

Variable	Low variability (n = 138)	Moderate variability (n = 137)	High variability (n = 137)	*p* value
Mean HbA1c, %	8.06	8.13	8.21	.602
Baseline eGFR, mL/min/1.73 m²	—	—	—	.140
Annual eGFR change, mL/min/1.73 m²/year	−0.84	−1.41	−1.74	<.001

Rapid renal decline, n (%)	1 (0.7)	6 (4.4)	13 (9.5)	.003

Note. More negative annual eGFR values indicate faster loss of kidney function.

Rapid Decline in Kidney Function

Rapid renal decline was observed in 20 of the 412 patients, corresponding to 4.9% of the study population. The frequency was not evenly distributed across the glycemic variability groups.

Only one patient (0.7%) in the low-variability group developed rapid renal decline. This increased to 6 patients (4.4%) in the moderate-variability group and 13 patients (9.5%) in the high-variability group.

The difference was statistically significant (p = .003). Therefore, patients with the greatest fluctuations in HbA1c were more likely to experience rapid deterioration in renal function.

This pattern was present even though the average HbA1c values were relatively similar between the three variability categories. It suggested that the stability of glucose control may carry additional information that is not fully reflected by a single average HbA1c value.

Relationship Between HbA1c Variability and eGFR Decline

Correlation analysis showed a moderate negative relationship between HbA1c coefficient of variation and annual eGFR change (r = −0.431, p < .001). As HbA1c variability increased, the annual decline in kidney function became greater.

The scatter plot also showed that patients with lower HbA1c variability were more commonly clustered around smaller reductions in eGFR. In contrast, larger falls in renal function became more frequent at higher levels of HbA1c variability.

Multivariable Analysis

A multivariable logistic regression model was used to assess factors associated with rapid renal decline. The model included HbA1c variability, mean HbA1c, age, duration of diabetes, hypertension, baseline eGFR, albuminuria, and body mass index.

HbA1c variability remained independently associated with rapid deterioration in kidney function. Each one-percentage-point increase in HbA1c coefficient of variation was associated with approximately 31% higher odds of rapid renal decline (adjusted OR = 1.31, 95% CI [1.14, 1.51], p < .001).

Mean HbA1c was also independently related to rapid renal deterioration (adjusted OR = 1.62, 95% CI [1.07, 2.46], p = .023). Increasing age showed a smaller but statistically significant relationship with the outcome (adjusted OR = 1.05, 95% CI [1.00, 1.11], p = .040).

Duration of diabetes, hypertension, baseline eGFR, albuminuria, and BMI did not reach statistical significance in the adjusted model.

Table 3. Multivariable logistic regression for rapid renal decline

Predictor	Adjusted OR	95% CI	*p* value
HbA1c coefficient of variation	1.31	1.14–1.51	<.001
Mean HbA1c	1.62	1.07–2.46	.023
Age	1.05	1.00–1.11	.040
Duration of diabetes	1.07	0.97–1.18	.161
Hypertension	1.95	0.58–6.57	.282
Baseline eGFR	1.02	0.99–1.05	.214
Albuminuria	0.60	0.21–1.72	.339
BMI	0.94	0.84–1.05	.257

Note. OR = odds ratio; CI = confidence interval; BMI = body mass index; eGFR = estimated glomerular filtration rate.

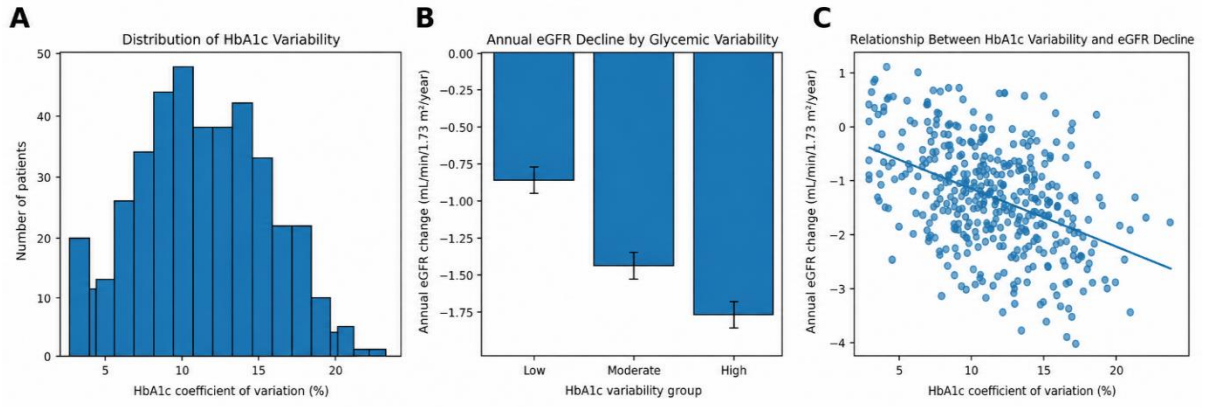


Figure 1. Glycemic variability and decline in kidney function. (A) Distribution of HbA1c coefficient of variation among study participants. (B) Mean annual change in estimated glomerular filtration rate (eGFR) across low, moderate, and high HbA1c variability groups; error bars represent standard error. (C) Relationship between HbA1c coefficient of variation and annual eGFR change, showing a negative association between glycemic variability and kidney function. More negative eGFR values indicate faster renal decline.

Summary of Findings

The findings showed a gradual increase in renal decline as glycemic variability increased. Participants in the highest HbA1c variability group lost kidney function at roughly twice the annual rate seen in the lowest variability group. They also had a substantially higher proportion of rapid renal decline.

The relationship remained significant after adjustment for mean HbA1c and several other clinical variables. In this cohort, HbA1c variability therefore appeared to provide additional information regarding the risk of kidney function deterioration beyond average HbA1c alone.

DISCUSSION

The main finding of this study was a clear relationship between long-term glycemic variability and deterioration of kidney function in patients with type 2 diabetes mellitus. Patients whose HbA1c changed more from one visit to another experienced a faster annual decline in eGFR. This pattern was gradual. Mean annual eGFR decline increased from −0.84 mL/min/1.73 m² in the low-variability group to −1.41 mL/min/1.73 m² in the moderate group and −1.74 mL/min/1.73 m² in patients with high variability. At the same time, rapid renal decline became more common as HbA1c variability increased. These findings suggest that the stability of glycemic control may matter in addition to the average HbA1c value.

This observation is in agreement with earlier longitudinal evidence. Lee et al. (2020) followed 1,383 patients with type 2 diabetes and reported progressively greater annual eGFR loss across increasing tertiles of HbA1c coefficient of variation. Their annual eGFR decline ranged from −0.99 mL/min/1.73 m² in the lowest variability group to −2.53 mL/min/1.73 m² in the highest group. Importantly, the same tendency was observed even in patients with HbA1c below 7%. This supports the finding in the present analysis that variation in HbA1c may identify renal risk that is not obvious from average HbA1c alone.

A similar conclusion was reached in a much larger cohort reported by Xu et al. (2023). Their study included 93,598 adults with diabetes and examined long-term visit-to-visit HbA1c variability in relation to kidney outcomes. Greater variability was associated with CKD progression, acute kidney injury and worsening albuminuria. The large size of that study is important because it shows that the relationship is not restricted to relatively small specialist cohorts. Instead, glycemic instability appears to have relevance across a broad population receiving routine diabetes care.

Another notable finding in our analysis was that mean HbA1c did not differ significantly between the low-, moderate-, and high-variability groups. Mean HbA1c values were approximately 8% in all three categories, yet renal decline differed considerably between them. This is clinically meaningful. HbA1c is usually interpreted as an overall measure of glycemic exposure, but two individuals with the same mean value may have very different glucose histories. One may remain around a fairly stable level, while another

repeatedly shifts between periods of good and poor control. Looking only at the average could therefore hide clinically important instability.

Evidence from systematic reviews supports this interpretation. Gorst et al. (2015) found that higher HbA1c variability was associated with renal disease and several other adverse outcomes independently of mean HbA1c. In patients with type 2 diabetes, greater variability was associated with a higher risk of renal disease, cardiovascular outcomes and mortality. More recently, Qu et al. (2022) examined different measurements of HbA1c variability, including standard deviation, coefficient of variation and HbA1c variability score. The highest categories of these variability measures were consistently associated with an increased risk of chronic kidney disease progression and other diabetic complications.

The present findings are also strengthened by the moderate negative correlation observed between HbA1c variability and annual eGFR change. Higher HbA1c coefficient of variation was accompanied by a greater loss of renal function ($r = -0.431$). Although correlation alone does not prove causation, the direction of the relationship fits well with previous longitudinal studies. Yan et al. (2022), for example, showed that visit-to-visit HbA1c variability had predictive value for the development of diabetic kidney disease. Their findings further suggest that repeated HbA1c measurements contain prognostic information that is not captured when only one value is considered.

The multivariable findings add another important point. HbA1c variability remained independently associated with rapid renal decline after adjustment for mean HbA1c and other clinical factors. In the present model, each one-percentage-point rise in HbA1c coefficient of variation was associated with approximately 31% higher odds of rapid decline in kidney function. Mean HbA1c itself was also associated with renal deterioration, indicating that average glycemic exposure remains important. The results therefore do not suggest replacing HbA1c targets with variability measures. Rather, the two measures may provide different but complementary information.

This interpretation is consistent with the ADVANCE trial analysis by Hirakawa et al. (2014). Greater visit-to-visit variability in HbA1c was associated with higher risks of vascular events and mortality after adjustment for relevant clinical variables. These findings helped establish the idea that fluctuations in glycemic control may carry prognostic importance beyond the absolute HbA1c concentration. The updated meta-analysis by Wang et al. (2024) further supports this view, concluding that greater HbA1c variability is associated with an increased risk of renal function decline in people with type 2 diabetes.

Several mechanisms may explain this relationship. Repeated changes between relatively high and lower glucose levels may produce greater oxidative stress and endothelial injury than a more stable glucose concentration. This may increase inflammatory activity and accelerate microvascular injury within the kidney. Glycemic variability may also reflect inconsistent medication adherence, irregular dietary intake, changes in treatment, recurrent illness or difficulty maintaining regular diabetes follow-up. It may therefore act partly as a biological risk factor and partly as a marker of unstable disease management.

The issue is especially relevant in Pakistan, where diabetic kidney disease already represents an important clinical burden. Islam et al. (2023) reported CKD in 32% of 203 patients with type 2 diabetes attending a tertiary care hospital in Pakistan. Ahmad et al. (2017) also documented a substantial burden of microalbuminuria among Pakistani patients with type 2 diabetes. However, most Pakistani studies have focused on existing CKD, albuminuria or single measurements of glycemic control rather than longitudinal HbA1c variability. This leaves an important local evidence gap.

Some limitations should be considered. HbA1c variability can be influenced by the number and timing of measurements, medication changes, anemia and other clinical conditions. Residual confounding is also possible in observational research. In addition, coefficient of variation is only one way of expressing long-term glycemic variability. Future studies could compare HbA1c standard deviation, variability independent of the mean, HbA1c variability score and continuous glucose monitoring measures.

Overall, these findings support the view that stable glycemic control may be as relevant as reaching an average HbA1c target. Patients who repeatedly move between high and lower HbA1c values may represent a group at greater risk for accelerated loss of renal function. Routine evaluation of visit-to-visit HbA1c variability may therefore offer a simple additional method for identifying patients who need closer renal monitoring and more consistent diabetes management.

CONCLUSION

This study suggests that long-term glycemic variability may play an important role in the decline of kidney function among patients with type 2 diabetes mellitus. Patients with greater visit-to-visit changes in HbA1c showed a faster reduction in eGFR and a higher frequency of rapid renal decline. This pattern was seen even when the average HbA1c values were relatively similar between groups.

The findings support the idea that mean HbA1c alone may not fully describe the renal risk of a patient with diabetes. A patient may achieve an acceptable average HbA1c but still experience repeated fluctuations over time, and these fluctuations may be clinically important. Monitoring the stability of glycemic control may therefore provide additional information when assessing the risk of diabetic kidney disease progression.

In routine practice, repeated HbA1c values should not only be viewed as separate results. Their pattern over time may also be useful. Patients with marked glycemic variability may benefit from closer follow-up, review of treatment adherence, dietary counseling, medication adjustment, and more frequent monitoring of renal function.

Further prospective studies using real-world data from Pakistani populations are needed to confirm this relationship and determine the most practical measure of glycemic variability for clinical use. If confirmed, incorporating HbA1c variability into routine diabetes care may help identify patients at greater risk of renal deterioration at an earlier stage.

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