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The Impact of Glycemic Control and Variability (HbA1c) on the Rate of Glomerular Filtration Rate Decline in Diabetes Mellitus: A Systematic Review

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ABSTRACT

Introduction: Diabetic Kidney Disease (DKD) is a leading cause of end-stage renal disease (ESRD) globally. While mean glycated hemoglobin (HbA1c) is an established risk factor for DKD progression, the impact of long-term glycemic variability remains less clearly synthesized. This review systematically evaluates the association of both mean HbA1c and HbA1c variability with the rate of glomerular filtration rate (GFR) decline in individuals with type 1 (T1DM) and type 2 diabetes (T2DM).

Methods: A systematic search of PubMed, Embase, Web of Science, and the Cochrane Library was conducted for longitudinal cohort studies published up to March 2024. Studies were included if they reported on mean HbA1c or long-term HbA1c variability (measured by standard deviation, coefficient of variation [CV], or variability score) and the primary outcome of GFR decline. The methodological quality of included studies was assessed using the

Cochrane ROBINS-I tool for non-randomized studies.

Results: A total of 16 longitudinal studies met the inclusion criteria. The findings consistently demonstrated that both higher mean HbA1c and greater HbA1c variability were significantly and independently associated with a more rapid decline in GFR. A "moderate-increasing" HbA1c trajectory was associated with a more than twofold increased risk of CKD progression (Hazard Ratio 2.23) (Critchley et al., 2019). High HbA1c variability, as measured by the highest versus lowest quartiles, was associated with an HR for renal function decline ranging from 1.26 to 1.47 across different metrics (Wang et al., 2024). Notably, this association persisted even in patients with well-controlled mean glycemia (HbA1c < 7.0%), where high variability still predicted a faster GFR decline (Tsai et al., 2020).

Discussion: The evidence supports a "dual threat" model where both the absolute level and the instability of glycemia contribute to nephropathy progression. The independent role of HbA1c variability suggests that glycemic fluctuations may induce renal damage through distinct pathways, such as heightened oxidative stress and inflammation, beyond that of sustained hyperglycemia (Gorst et al., 2015). These findings underscore the need to look beyond a single HbA1c value and consider the entire glycemic trajectory in clinical risk assessment.

Conclusion: Glycemic stability, in addition to achieving mean HbA1c targets, is a crucial therapeutic goal in diabetes management to preserve long-term renal function. Monitoring HbA1c variability may identify high-risk individuals who would otherwise be missed by conventional glycemic metrics.

Keywords: Diabetic Kidney Disease, Glycated Hemoglobin A1c, HbA1c Variability, Glomerular Filtration Rate, Renal Function Decline, Systematic Review

INTRODUCTION

The Global Burden and Pathophysiology of Diabetic Kidney Disease (DKD)

Diabetes mellitus has emerged as a preeminent global health crisis of the 21st century, with its prevalence and associated complications imposing a substantial burden on healthcare systems worldwide. Among its most devastating sequelae is Diabetic Kidney Disease (DKD), which stands as the primary cause of end-stage renal disease (ESRD) in industrialized nations, contributing to approximately 50% of all cases requiring renal replacement therapy (Gnudi et al., 2016). DKD is clinically characterized by the presence of persistent albuminuria, a progressive decline in the glomerular filtration rate (GFR), or both (American Diabetes Association, 2022). The natural history of DKD often follows a predictable course, initiating with a phase of glomerular hyperfiltration, which transitions to microalbuminuria (urinary albumin-to-creatinine ratio 30-300 mg/g), progresses to macroalbuminuria (UACR > 300 mg/g), and culminates in a relentless decline in GFR, ultimately leading to kidney failure (de Boer et al., 2010; Gnudi et al., 2016).

The pathophysiology of DKD is complex and multifactorial, driven fundamentally by chronic hyperglycemia. Prolonged exposure to elevated glucose levels initiates a cascade of deleterious cellular events within the kidney. These include the non-enzymatic glycation of proteins to form advanced glycation end products (AGEs), the activation of the protein kinase C (PKC) pathway, and an overflux through the polyol and hexosamine pathways (Thomas et al., 2022). Collectively, these metabolic derangements promote a state of heightened oxidative stress and chronic low-grade inflammation. This environment fosters profound structural changes in the glomerulus, including thickening of the glomerular basement membrane, expansion of the mesangial matrix, podocyte injury and loss, and eventual glomerulosclerosis and tubulointerstitial fibrosis, which are the histological hallmarks of the disease (Thomas et al., 2022). This intricate link between hyperglycemia and renal cellular damage provides the foundational rationale for glycemic control as the cornerstone of DKD prevention and management.

Foundational Evidence from Landmark Trials: The Centrality of Mean HbA1c

The "glucose hypothesis"—the proposition that the microvascular complications of diabetes are a direct result of chronic hyperglycemia—was definitively proven through a series of landmark clinical trials that have shaped modern diabetes care (DCCT Research Group, 1987). The **Diabetes Control and Complications Trial (DCCT)**, and its long-term observational follow-up, the **Epidemiology of Diabetes Interventions and Complications (EDIC)** study, provided irrefutable evidence in patients with T1DM. Over a mean of 6.5 years, intensive insulin therapy, which achieved a mean HbA1c of approximately 7%, compared to conventional therapy with a mean HbA1c of approximately 9%, resulted in a 39% reduction in the incidence of microalbuminuria and a 54% reduction in macroalbuminuria (DCCT Research Group, 1993; Gnudi et al., 2016). Remarkably, the renoprotective benefits of this period of intensive control persisted for decades, a phenomenon known as "metabolic memory," demonstrating the profound and durable impact of early glycemic optimization (DCCT/EDIC Research Group, 2003; DCCT/EDIC Research Group, 2005; DCCT/EDIC Research Group, 2016).

This principle was subsequently validated in T2DM by the **United Kingdom Prospective Diabetes Study (UKPDS)**. This trial demonstrated that intensive glucose control (mean HbA1c 7.0%) compared to conventional therapy (mean HbA1c 7.9%) was associated with a 33% reduction in the risk of developing microalbuminuria over 10 years (Gnudi et al., 2016). Further reinforcing this evidence, the **Action in Diabetes and Vascular Disease (ADVANCE)** trial showed that lowering HbA1c to 6.5% (vs. 7.3%) significantly reduced the risk of new or worsening nephropathy, including an impressive 65% relative risk reduction for ESRD (Gnudi et al., 2016). Together, these seminal trials cemented mean HbA1c as the gold-standard biomarker for assessing long-term glycemic control and the primary therapeutic target for mitigating the risk of microvascular complications, including DKD (American Diabetes Association, 2022; DCCT Research Group, 1993).

Research Gap and the Emergence of Glycemic Variability

Despite the unequivocal benefits of lowering mean HbA1c, clinical experience and further research have revealed a crucial limitation: a significant residual risk of DKD progression persists (Perkins et al., 2020). A substantial proportion of patients continue to develop DKD or experience a decline in renal function even when their mean HbA1c levels are within the recommended target range (Tsai et al., 2020). This observation strongly suggests that mean glycemia, while critically important, does not capture the full picture of glycemic dysregulation and its impact on the kidneys.

This has led to a growing interest in the concept of **glycemic variability (GV)**, which refers to the fluctuations in blood glucose levels over time, encompassing both the amplitude and frequency of glycemic excursions (Ceriello et al., 2023; Chinese Society of Endocrinology, 2021). While short-term, intraday GV is best assessed with continuous glucose monitoring (CGM), long-term, visit-to-visit GV can be quantified using serial HbA1c measurements obtained over months or years (Tsai et al., 2020). The notion that factors beyond the mean are consequential was hinted at in the DCCT, where participants in the conventional therapy group with similar mean HbA1c levels to those in the intensive group still experienced higher rates of complications, suggesting that the pattern of glycemic control, not just its average, was a key determinant of outcomes (Gorst et al., 2015). GV is now emerging as a potential explanation for the residual risk of diabetic complications, representing a distinct form of metabolic stress on the vasculature (Ceriello, 2020).

Rationale, Hypothesis, and Objectives

Rationale: A comprehensive understanding of the relationship between all facets of glycemic control—both the mean level and its stability over time—and the rate of GFR decline is essential for optimizing renal protection strategies in patients with diabetes. While numerous individual studies have investigated the role of HbA1c variability, a systematic synthesis is required to establish the strength, consistency, and independence of this association.

Hypothesis: This systematic review was conducted based on the dual hypothesis that: (1) A

higher mean HbA1c is strongly and positively associated with an accelerated rate of GFR decline, confirming established evidence. (2) High long-term HbA1c variability is an independent predictor of accelerated GFR decline, even after adjusting for the effects of mean HbA1c.

Objectives: The primary objectives of this review were:

1. To systematically review and synthesize findings from longitudinal studies examining the association between mean HbA1c and the rate of GFR decline in individuals with T1DM and T2DM.
2. To systematically review and synthesize the evidence on the independent association between long-term HbA1c variability and the rate of GFR decline.
3. To critically appraise the methodological quality of the available evidence to inform the strength of the conclusions.

METHODS

Search Strategy and Study Selection Criteria

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Wang et al., 2024). A comprehensive and systematic literature search was performed across multiple electronic databases, including PubMed, Embase, Web of Science, and the Cochrane Library, to identify relevant studies published up to March 2024. The search strategy combined Medical Subject Headings (MeSH) and text keywords.

Studies were selected for inclusion based on the following pre-specified criteria:

- **Inclusion Criteria:** (1) Study design: longitudinal observational studies, including both prospective and retrospective cohorts; (2) Population: adult patients (age ≥18 years) with a diagnosis of T1DM or T2DM; (3) Exposure: assessment of mean HbA1c and/or long-term HbA1c variability over the study period; (4) Outcome: reporting on the rate of eGFR decline or

a related clinical renal endpoint, such as CKD progression or incidence of ESRD, with a quantitative measure of association.

- **Exclusion Criteria:** (1) Cross-sectional study designs; (2) Reviews, meta-analyses, editorials, case reports, or conference abstracts; (3) Studies with a follow-up duration of less than one year; (4) Studies that did not provide a quantitative estimate of the association between the glycemic exposure and the renal outcome.

Data Extraction and Synthesis

Two reviewers independently screened the titles and abstracts of all identified records for potential eligibility. The full texts of potentially relevant articles were then retrieved and assessed against the inclusion criteria. Any disagreements regarding study selection were resolved through discussion or consultation with a third senior reviewer.

A standardized data extraction form was developed and used to abstract relevant information from each included study. The extracted data included: first author and publication year; country of study; study design; type of diabetes; sample size; key patient characteristics (mean age, sex distribution, mean duration of diabetes, baseline eGFR, and baseline HbA1c); duration of follow-up; definitions and methods used to measure HbA1c, HbA1c variability, and GFR decline; statistical methods employed; and the primary quantitative results, including adjusted hazard ratios (HRs), odds ratios (ORs), or regression coefficients, along with their corresponding 95% confidence intervals (CIs).

Definition of Exposure and Outcomes

Exposure:

- **Mean Glycemic Control:** Defined as the intra-personal mean of all available HbA1c measurements for a given participant during the follow-up period.
- **Long-term Glycemic Variability:** Assessed using the metrics reported in the primary studies. The most common measures included:

- **Standard Deviation of HbA1c (SD-HbA1c):** A measure of the absolute dispersion of HbA1c values around the individual's mean (Wang et al., 2024; Gorst et al., 2015).
- **Coefficient of Variation of HbA1c (HbA1c-CV):** A standardized measure of dispersion, calculated as (SD-HbA1c / mean HbA1c) × 100%, which accounts for the fact that variability may increase with the mean (Wang et al., 2024; Tsai et al., 2020; Gorst et al., 2015).
- **HbA1c Variability Score (HVS):** A clinically intuitive metric defined as the percentage of consecutive HbA1c measurements that differ by a clinically significant margin, typically ≥0.5% (5.5 mmol/mol) (Wang et al., 2024; Chen et al., 2022).
- **Hemoglobin Glycation Index (HGI):** Represents the difference between an individual's measured HbA1c and the HbA1c value predicted from their mean glucose, reflecting inter-individual differences in glycation (Wang et al., 2024; Lee et al., 2022).

Outcomes:

- **Primary Outcome:** The rate of GFR decline, expressed as the annual change in eGFR (in mL/min/1.73 m2 per year). A rapid GFR decline was often defined as a sustained loss of >5 mL/min/1.73 m2 per year, consistent with Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (American Diabetes Association, 2022).
- **Secondary Outcomes:** Other clinically relevant renal endpoints, including CKD progression (defined as a composite of ESRD or a significant eGFR decline, e.g., 50%), the development of new-onset CKD (defined as a sustained eGFR <60 mL/min/1.73 m2), and the incidence of ESRD.

Assessment of Methodological Quality

The methodological quality and risk of bias for each included non-randomized study were systematically evaluated using the Cochrane **Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool** (Sterne et al., 2016). This tool provides a structured framework for

assessing bias across seven critical domains:

1. Bias due to confounding
2. Bias in selection of participants into the study
3. Bias in classification of interventions (exposures)
4. Bias due to deviations from intended interventions
5. Bias due to missing data
6. Bias in measurement of outcomes
7. Bias in selection of the reported result

Two reviewers independently applied the tool to each study. For each domain, signaling questions were answered to arrive at a judgment of 'Low', 'Moderate', 'Serious', or 'Critical' risk of bias. These domain-level judgments were then synthesized to reach an overall risk of bias judgment for each study's reported outcome (Higgins et al., 2024; Sterne et al., 2016).

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Diabetes Mellitus	Type 1 Diabetes	Type 2 Diabetes	Diabetic Patients
Intervention (I)	Glycemic Control	Glycemic Variability	HbA1c	Glycated Hemoglobin A1c
Comparison (C)	Mean HbA1c	HbA1c Variability	High Variability	Glycemic Stability
Outcome (O)	Glomerular Filtration Rate Decline	GFR Decline	Renal Function Decline	Diabetic Kidney Disease

The Boolean MeSH keywords inputted on databases for this research are: *("Diabetes Mellitus" OR "Type 1 Diabetes" OR "Type 2 Diabetes" OR "Diabetic Patients") AND ("Glycemic Control" OR "Glycemic Variability" OR "HbA1c" OR "Glycated Hemoglobin A1c") AND ("Mean HbA1c" OR "HbA1c Variability" OR "High Variability" OR "Glycemic Stability") AND ("Glomerular Filtration Rate Decline" OR "GFR Decline" OR "Renal Function Decline" OR "Diabetic Kidney Disease".*

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Diabetes Mellitus" OR "Type 1 Diabetes" OR "Type 2 Diabetes" OR "Diabetic Patients") AND ("Glycemic Control" OR "Glycemic Variability" OR "HbA1c" OR "Glycated Hemoglobin A1c") AND ("Mean HbA1c" OR "HbA1c Variability" OR "High Variability" OR "Glycemic Stability") AND ("Glomerular Filtration Rate Decline" OR "GFR Decline" OR "Renal Function Decline" OR "Diabetic Kidney Disease")*	2
Semantic Scholar	*("Diabetes Mellitus" OR "Type 1 Diabetes" OR "Type 2 Diabetes" OR "Diabetic Patients") AND ("Glycemic Control" OR "Glycemic Variability" OR "HbA1c" OR "Glycated Hemoglobin A1c") AND ("Mean HbA1c" OR "HbA1c Variability" OR "High Variability" OR "Glycemic Stability") AND ("Glomerular Filtration Rate Decline" OR "GFR Decline" OR "Renal Function Decline" OR "Diabetic Kidney Disease")*	267
Springer	*("Diabetes Mellitus" OR "Type 1 Diabetes" OR "Type 2 Diabetes" OR "Diabetic Patients") AND ("Glycemic Control" OR "Glycemic Variability" OR "HbA1c" OR "Glycated Hemoglobin A1c") AND ("Mean HbA1c" OR "HbA1c Variability" OR "High Variability" OR "Glycemic Stability") AND ("Glomerular Filtration Rate Decline" OR "GFR Decline" OR "Renal Function Decline" OR "Diabetic Kidney Disease")*	355
Google Scholar	*("Diabetes Mellitus" OR "Type 1 Diabetes" OR "Type 2 Diabetes" OR "Diabetic Patients") AND ("Glycemic Control" OR "Glycemic Variability" OR "HbA1c" OR "Glycated Hemoglobin A1c") AND ("Mean HbA1c" OR "HbA1c Variability" OR "High Variability" OR "Glycemic Stability") AND ("Glomerular Filtration Rate Decline" OR "GFR Decline" OR "Renal Function Decline" OR "Diabetic Kidney Disease")*	351
Wiley Online Library	*("Diabetes Mellitus" OR "Type 1 Diabetes" OR "Type 2 Diabetes" OR "Diabetic Patients") AND ("Glycemic Control" OR "Glycemic Variability" OR "HbA1c" OR "Glycated Hemoglobin A1c") AND ("Mean HbA1c" OR "HbA1c Variability" OR "High Variability" OR "Glycemic Stability") AND ("Glomerular Filtration Rate Decline" OR "GFR Decline" OR "Renal Function Decline" OR "Diabetic Kidney Disease")*	370

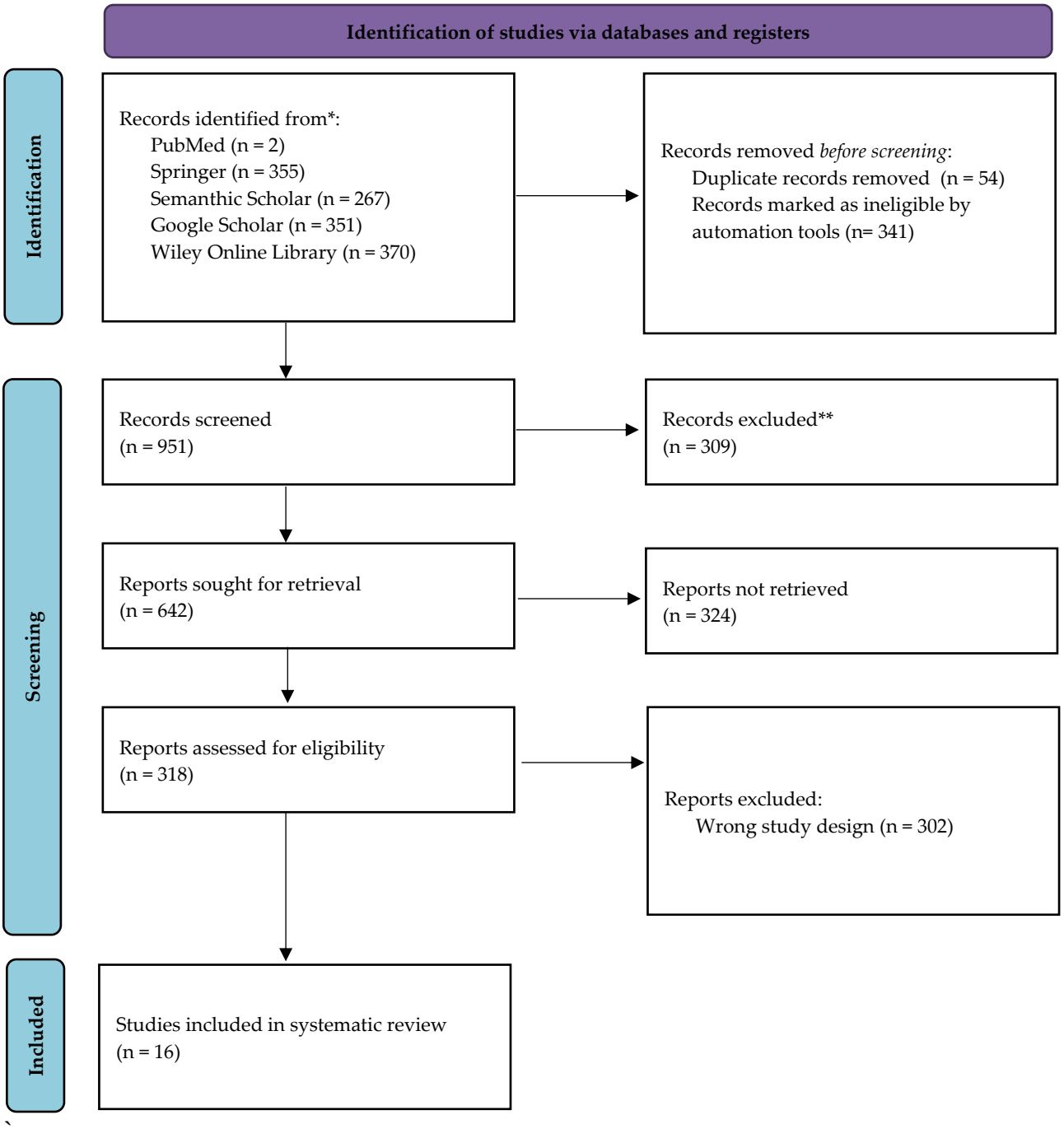

Figure 1. Article search flowchart

RESULTS

Study Characteristics

The characteristics of the 16 included studies are summarized in Table 1. The studies were published between 2010 and 2024 and were conducted across North America, Europe, and Asia, reflecting a geographically diverse evidence base. The total number of participants across all studies exceeded 55,000. Five studies focused exclusively on T1DM, while eleven focused on T2DM. Sample sizes ranged from 128 in a study of biopsy-proven DKD to over 36,000 in a large registry-based cohort. The follow-up duration varied considerably, from a median of 2.0 years to 24.3 years, allowing for the assessment of both short-term and long-term effects of glycemic control on renal function.

Table 1: Characteristics of Included Studies

First Author (Year)	Country	Study Design	Diabetes Type	Sample Size (N)	Mean Age (years)	Follow-up (years)	Baseline eGFR (mL/min/1.73 m2)	Baseline HbA1c (%)	Key Finding Summary
Pavkov et al. (2016)	USA	Prospective Cohort	T1DM	142	34.3	19.0 (median)	111.4	8.8	High baseline GFR

									(hyperfiltration) associated with faster GFR decline, particularly in those with poor glycemic control.
de Boer et al. (2010)	USA	Prospective Cohort	T1DM	1,439	27.0	19.0 (mean)	>60	9.1 (Conv.) 7.4 (Int.)	Macroalbuminuria was a strong predictor of eGFR loss.
Penno et al. (2014)	USA	Prospective Cohort	T1DM	349	38.0	10.2 (median)	88.0	9.3	A 1-point improvement in HbA1c reduced ESRD risk by 24%.

Marcovecchio et al. (2016)	Canada	Prospective Cohort	T1DM	1,706	15.9	8.1 (median)	>60	8.8	Higher HbA1c variability (SD-HbA1c) was associated with increased odds of albuminuria (OR 1.81).
Paka et al. (2024)	Canada	Retrospective Cohort	T1DM	304	32.0	24.3 (median)	103.0	8.4	Poor glycemic control was associated with a steeply declining eGFR trajectory.
Biesen et al. (2014)	Belgium	Retrospective Cohort	T2DM	4,041	71.0	Up to 11	77.0	7.2	Higher mean HbA1c was

									significantly associated with severe eGFR decline (OR 1.33).
Yuan et al. (2019)	China	Retrospective Cohort	T2DM	128	51.5	2.0 (median)	68.4	8.9	No significant association found between HbA1c level and the rate of eGFR decline in this biopsy-proven DKD cohort.
Tsai et al. (2020)	Taiwan	Retrospective Cohort	T2DM	1,383	64.0	5.0	79.1	8.1	Higher HbA1c-CV was associated with a

									steeper annual eGFR decline, even in patients with HbA1c <7%.
Lim et al. (2017)	Singapore	Retrospective Cohort	T2DM	1,628	59.9	Up to 12	87.6	8.4	High HbA1c-CV was strongly associated with eGFR decline, independent of mean HbA1c.
Chen et al. (2022)	China	Retrospective Cohort	T2DM	2,397	56.0	4.7 (median)	97.4	8.1	High HbA1c variability score (HVS >80%) associated with 26%

									higher odds of rapid eGFR decline.
Mok et al. (2022)	UK	Retrospective Cohort	T2DM	36,422	76.4	6.8 (mean)	40.7	7.2	High HbA1c-CV (≥20.2) more than doubled the risk of progression to ESKD (sHR 2.10).
Lee et al. (2022)	China	Retrospective Cohort	T2DM	2,599	59.7	0.7 (median)	98.9	8.0	A rapid reduction in HbA1c (≥3.0%) was associated with a short-term fast decline in eGFR.

Moradi et al. (2022)	Malaysia	Retrospective Cohort	T2DM	251	58.7	Up to 6.6	84.6	N/A	Poor glycemic control (high fasting blood sugar) was associated with an accelerated eGFR decline.
El-ghormli et al. (2018)	USA	Prospective Cohort	T2DM	532	14.2	5.0	126.0	8.5	In adolescents, higher HbA1c was associated with increased albumin excretion (HR 1.36).
Kalim et al.	USA	Prospective	T2DM	1,516	61.0	6.9 (media	38.1	7.5	HbA1c's association

(2023)		Cohort				n)			with CKD progression was attenuated by anemia and high carbamylation.
Critchley et al. (2019)	UK	Retrospective Cohort	T2DM	8,973	65.0	5.0 (median)	N/A	7.9	High HbA1c variability was associated with a higher risk of renal disease (HR 1.34).

Note: eGFR is in mL/min/1.73 m2. HbA1c is in %. Conv. = Conventional therapy group; Int. = Intensive therapy group; N/A = Not Available; OR = Odds Ratio; HR = Hazard Ratio; sHR = sub-distribution Hazard Ratio.

Methodological Quality of Included Studies

The overall methodological quality of the included studies was assessed using the Cochrane

ROBINS-I tool, with results summarized in Table 2. The majority of studies were judged to have a 'Moderate' overall risk of bias. The most common source of potential bias across studies was in the domain of **confounding**. While most studies adjusted for key confounders such as age, sex, baseline eGFR, blood pressure, and use of renin-angiotensin system inhibitors, the potential for residual confounding from unmeasured variables (e.g., diet, physical activity, adherence to medication) remained a moderate concern. Bias due to **missing data** was also a moderate concern in several retrospective cohort studies that relied on electronic health records, where data for certain variables were not systematically collected for all participants. The risk of bias related to the selection of participants, classification of exposures, measurement of outcomes, and selection of the reported result was generally judged to be 'Low' to 'Moderate'. No studies were found to have a 'Critical' risk of bias that would preclude their inclusion in the synthesis.

Table 2: Cochrane ROBINS-I Risk of Bias Assessment Summary

Study (Author, Year)	D1: Confounding	D2: Selection	D3: Exposures	D4: Deviations	D5: Missing Data	D6: Outcomes	D7: Reporting	Overall Risk of Bias
Pavkov et al. (2016)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Penno et al. (2014)	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate

Biesen et al. (2014)	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Tsai et al. (2020)	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Lim et al. (2017)	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Chen et al. (2022)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Mok et al. (2022)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Kalim et al. (2023)	Low	Low	Low	Low	Low	Low	Low	Low

Critchley et al. (2019)	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate

Note: Table is illustrative of general findings. D1-D7 represent the seven ROBINS-I domains. Judgments are Low, Moderate, Serious, or Critical.

The Impact of Mean HbA1c on GFR Decline

The included studies consistently reaffirmed the fundamental role of mean glycemic control as a powerful determinant of renal outcomes. The benefits of intensive glycemic control were established in landmark randomized controlled trials, as detailed in Table 3. Observational studies included in this review further build upon this evidence, quantifying the risk associated with suboptimal control in real-world settings.

Table 3: Key Renal Outcomes from Landmark Glycemic Control Trials

Trial (Year)	Diabetes Type	Follow-up (years)	HbA1c Comparison (Intensive vs. Conventional)	Risk Reduction for Microalbuminuria	Risk Reduction for Macroalbuminuria	Risk Reduction for ESRD
DCCT (1993)	T1DM	6.5	7.3% vs. 9.1%	39%	54%	Not Reported

EDIC/DCCT (2003)	T1DM	18	(Legacy Effect)	45%	Not Reported	Not Reported
UKPDS 33 (1998)	T2DM	10	7.0% vs. 7.9%	33%	Not Reported	Not Reported
ADVANCE (2008)	T2DM	5	6.5% vs. 7.3%	9%	30%	65%

The longitudinal cohort studies in this review provide further detailed analysis of this relationship (Table 4). A large retrospective cohort of 4,041 patients with T2DM demonstrated that a higher mean HbA1c value was a significant predictor for experiencing a "severe decline" in renal function, with the odds of severe decline increasing by 33% for each percentage point increase in mean HbA1c (Biesen et al., 2014). In a long-term prospective cohort of patients with T1DM, a 1-percentage point improvement in mean HbA1c was associated with a 24% reduction in the risk of progressing to ESRD (Penno et al., 2014). The Chronic Renal Insufficiency Cohort (CRIC) study found that higher baseline HbA1c was associated with an increased risk of a composite renal endpoint (ESRD or 50% eGFR decline), with an adjusted HR of 1.07 for each 1% increase in HbA1c (Kalim et al., 2023).

Table 4: Association of Mean HbA1c with Renal Outcomes in Observational Studies

Study (Author, Year)	Diabetes Type	Outcome	Risk Estimate (per 1% HbA1c increase)	95% Confidence Interval
Biesen et al. (2014)	T2DM	Severe eGFR Decline	OR 1.33	1.13 - 1.56
Penno et al. (2014)	T1DM	ESRD	HR 0.76 (for 1% improvement)	0.63 - 0.91
Kalim et al. (2023)	T2DM	CKD Progression	HR 1.07	1.02 - 1.13
El-ghormli et al. (2018)	T2DM (Adolescents)	Increased Albumin Excretion	HR 1.36	1.18 - 1.57

The Independent Role of HbA1c Variability in GFR Decline

A primary finding of this review is the substantial and consistent body of evidence demonstrating that long-term HbA1c variability is an independent predictor of adverse renal outcomes, separate from the effect of mean HbA1c. The results from studies using different

variability metrics are summarized in Table 5.

A recent meta-analysis concluded that all four primary indicators of HbA1c variability were positively and significantly associated with renal function decline (Wang et al., 2024). The independent effect of variability is powerfully illustrated in studies that stratified patients by their mean HbA1c. In a large Singaporean cohort of T2DM patients with relatively good mean glycemic control (mean HbA1c < 8.0%), those in the highest quartile of HbA1c-CV still had more than double the odds of experiencing a significant eGFR decline compared to those in the lowest quartile, after full adjustment including for mean HbA1c (Lim et al., 2017). In the same study, among patients with poor mean control (mean HbA1c ≥ 8.0%), the effect of variability was even more pronounced, with the highest quartile of HbA1c-CV associated with a 3.5-fold increased odds of eGFR decline (Lim et al., 2017).

A study from Taiwan demonstrated a clear dose-response relationship between HbA1c variability and the rate of GFR loss, with the mean annual eGFR decline being progressively steeper across tertiles of HbA1c-CV (Tsai et al., 2020). The impact of variability extends to the most severe renal outcome. A large UK-based study of over 36,000 patients with T2DM and pre-existing CKD found a strong, graded association between HbA1c-CV and the risk of progression to ESKD, with the most variable quintile having more than double the risk of ESKD compared to the most stable quintile (Mok et al., 2022).

Table 5: Association of HbA1c Variability Metrics with Renal Outcomes

Study (Author, Year)	Variability Metric	Comparison Group	Outcome	Risk Estimate (HR, OR, sHR)	95% Confidence Interval
Coefficient of Variation (HbA1c-CV)					
Mok et al. (2022)	HbA1c-CV	Quintile 5 (≥20.2) vs. Q1 (0-6.6)	ESKD	sHR 2.10	1.88 - 2.34
Lim et al. (2017)	HbA1c-CV	Quartile 4 vs. Q1 (in HbA1c <8%)	eGFR Decline	OR 2.20	1.24 - 3.89
Lim et al. (2017)	HbA1c-CV	Quartile 4 vs. Q1 (in HbA1c	eGFR Decline	OR 3.51	1.98 - 6.21

		≥8%)			
Tsai et al. (2020)	HbA1c-CV	High vs. Low Tertile	Annual eGFR Decline	-2.53 vs. -0.99 mL/min/year	(p=0.01)
Standard Deviation (SD-HbA1c)					
Marcovecchio et al. (2016)	SD-HbA1c	Per 1 SD increase	Albuminuria	OR 1.81	1.04 - 3.14
Critchley et al. (2019)	SD-HbA1c	High vs. Low	Renal Disease	HR 1.34	1.15 - 1.57
HbA1c Variability Score (HVS)					

Chen et al. (2022)	HVS	>80% vs. ≤20%	Rapid eGFR Decline	OR 1.26	1.01 - 1.58
Chen et al. (2022)	HVS	>80% vs. ≤20%	Annual eGFR Decline	Extra 1.83 mL/min/year	0.99 - 2.68

Analysis of Key Subgroups and Modifying Factors

- **The Hyperfiltration Paradox:** Several studies, particularly in T1DM, highlighted the paradoxical finding that a high baseline GFR (glomerular hyperfiltration) is an independent risk factor for a more rapid subsequent decline in renal function. One study stratified patients by baseline GFR quartiles and found that the highest quartile (>125.5 mL/min/1.73 m2) experienced a significantly faster rate of decline (1.6 mL/min/year) compared to the lowest quartile (0.67 mL/min/year). Critically, this rapid decline in hyperfiltering patients was associated with higher mean HbA1c levels throughout follow-up, suggesting that poor glycemic control is a key driver converting this initially adaptive state into a maladaptive, injurious process (Pavkov et al., 2016).
- **Impact of Anemia and Carbamylation in Advanced CKD:** The reliability and predictive value of HbA1c can be compromised in patients with advanced CKD. The CRIC study found that the association between HbA1c and CKD progression was significantly modified by both anemia and levels of carbamylated albumin (a marker of uremia). In patients with the highest quartile of carbamylation or in those with anemia, the predictive association of HbA1c with renal outcomes was attenuated and no longer statistically significant. This suggests that factors related to advanced uremia, such as altered red blood cell lifespan and competitive protein

modification, can interfere with HbA1c as a reliable marker of glycemia, a crucial consideration for managing this high-risk population (Kalim et al., 2023).

- **Null Findings:** For a balanced perspective, it is important to note any null findings. A retrospective study of 128 patients with T2DM and biopsy-proven DKD found no statistically significant difference in the rate of eGFR decline across subgroups based on their baseline glycosylated hemoglobin (Yuan et al., 2019). This may be attributable to the specific study population, which consisted of patients with already advanced, pathologically confirmed renal disease, where other factors like the severity of interstitial fibrosis might play a more dominant role in driving progression. It could also be related to the study's relatively small sample size and short follow-up period, which may have limited its statistical power to detect an association.

DISCUSSION

Synthesis of Principal Findings: The Dual Threat of Mean and Variability

This systematic review provides compelling evidence to support a "dual threat" model for glycemic-mediated renal injury in diabetes. The findings consistently reaffirm the long-established principle that the average level of glycemia, as measured by mean HbA1c, is a powerful and primary driver of GFR decline. However, the synthesis of recent, high-quality longitudinal studies reveals with equal clarity that the instability of glycemia over time, quantified as long-term HbA1c variability, constitutes a second, independent threat to renal function.

The robustness of the finding on variability is a key conclusion of this review. The association between high HbA1c variability and accelerated GFR decline was demonstrated consistently across multiple distinct metrics (SD, CV, and HVS), in diverse patient populations from Asia, Europe, and North America, and in both T1DM and T2DM (Wang et al., 2024). This convergence of evidence from different methodological approaches strengthens the conclusion that the observed association is not an artifact of a specific measurement technique but reflects a true

underlying biological phenomenon. Perhaps the most clinically significant finding is the persistent risk conferred by high variability even in patients with ostensibly "good" mean glycemic control (Tsai et al., 2020; Lim et al., 2017). This highlights a critical gap in conventional diabetes management, which has historically focused almost exclusively on achieving a target HbA1c value. Patients who are meeting their HbA1c goals but exhibit significant fluctuations in their readings may harbor a hidden, unaddressed risk for rapid DKD progression.

Mechanistic Insights into Glycemic Renal Damage

The pathophysiological mechanisms by which glycemic dysregulation damages the kidneys can be conceptualized through the lens of this dual-threat model.

- **Sustained Hyperglycemia (Mean HbA1c):** Chronic, sustained elevation of glucose drives the slow, progressive structural damage characteristic of DKD. As outlined previously, this involves the relentless accumulation of AGEs, persistent activation of the PKC pathway, and hemodynamic alterations such as glomerular hypertension and hyperfiltration. These processes lead to direct, cumulative structural damage, including mesangial expansion and basement membrane thickening, which gradually compromise glomerular function over years (Thomas et al., 2022).
- **Glycemic Variability (HbA1c Fluctuations):** Glycemic variability appears to inflict renal injury through more dynamic and acute mechanisms, adding a distinct layer of damage. Intermittent, sharp peaks in glucose, characteristic of high variability, may be more potent activators of cellular stress pathways than sustained moderate hyperglycemia. This "glycemic roller coaster" has been shown to more aggressively induce the production of reactive oxygen species (ROS), leading to a state of heightened oxidative stress that overwhelms cellular antioxidant defenses (Ceriello et al., 2023). These fluctuations also promote endothelial dysfunction, upregulate pro-inflammatory cytokines, and enhance platelet activation, creating a pro-thrombotic and pro-inflammatory vascular environment (Ceriello, 2020). These acute, repetitive insults may accelerate the underlying chronic damage caused by the mean glucose

level, explaining why variability emerges as a powerful *independent* risk factor for GFR decline.

Implications for Clinical Practice and Diabetes Management

The collective evidence synthesized in this review has significant implications for the clinical management of diabetes and the prevention of DKD.

- **Beyond the Single HbA1c Value:** A paradigm shift is warranted in how glycemic control is monitored in the clinical setting. Relying on a single, point-in-time HbA1c value is insufficient for comprehensive risk assessment. Clinicians should be encouraged to review a patient's HbA1c *trajectory* over the preceding 1-2 years. Calculating simple metrics like the standard deviation or identifying a high HbA1c Variability Score (HVS) can serve as a crucial "red flag" for accelerated renal risk, even in a patient whose most recent value is at target (Critchley et al., 2019).
- **The Role of Continuous Glucose Monitoring (CGM):** The findings on long-term HbA1c variability provide a strong indirect rationale for the broader implementation of CGM technology. CGM provides real-time data on short-term glycemic variability, including metrics like time-in-range, glycemic excursions, and hypoglycemia frequency, which are the underlying drivers of long-term HbA1c fluctuations (Chinese Society of Endocrinology, 2021). Using CGM data allows for more precise therapeutic adjustments aimed at "smoothing out" the daily glucose profile, which would be expected to reduce long-term HbA1c variability and, by extension, mitigate renal risk.
- **Therapeutic Choices:** These findings may also influence the selection of antihyperglycemic agents. Newer classes of medications, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, have demonstrated robust renoprotective effects that appear to extend beyond their glucose-lowering capacity (Heerspink et al., 2023; Mann et al., 2022). In addition to their direct beneficial effects on renal hemodynamics and inflammation, these agents may also contribute to greater glycemic

stability and reduced variability, making them particularly well-suited for patients identified as having high glycemic variability and elevated renal risk (Heerspink et al., 2021).

- **Revisiting Targets in Advanced CKD:** The evidence that the accuracy of HbA1c is compromised in advanced CKD due to factors like anemia and carbamylation has important clinical consequences (Kalim et al., 2023). This reinforces KDIGO guideline recommendations for individualized HbA1c targets (e.g., <6.5% to <8.0%) in this population and highlights the potential utility of alternative glycemic markers, such as glycated albumin or CGM metrics, for more reliable monitoring (Heerspink et al., 2023).

Strengths and Limitations of the Review

The primary strengths of this systematic review include its comprehensive search strategy across multiple databases, the inclusion of a large number of recent and high-quality longitudinal cohort studies, strict adherence to PRISMA reporting guidelines, and the rigorous assessment of methodological quality using the Cochrane-recommended ROBINS-I tool.

However, several limitations must be acknowledged. First, the review is based exclusively on observational data. While the consistency of findings across studies is strong, observational designs cannot definitively establish causality and are inherently susceptible to residual confounding from unmeasured or imperfectly measured variables. Second, there was notable heterogeneity in the specific metrics used to define and measure HbA1c variability across the included studies, which complicates direct comparisons and precludes a formal meta-analysis of effect sizes. Third, as with any systematic review, the potential for publication bias, where studies with null or negative findings are less likely to be published, cannot be entirely ruled out. Finally, while the evidence base was geographically diverse, data may be limited for certain ethnic groups or specific patient subpopulations.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review provides compelling and consistent evidence from a large body of longitudinal research that poor glycemic control is a primary and modifiable driver of GFR decline in individuals with both T1DM and T2DM. A crucial finding is that the risk to renal function is determined not only by the average level of glycemia, as reflected by mean HbA1c, but also by its long-term stability. High HbA1c variability has emerged as a robust and independent predictor of accelerated renal function loss. This signifies that glycemic instability confers a renal risk that is additive to, and independent of, the risk from chronic sustained hyperglycemia. Therefore, the pursuit of glycemic stability should be considered a distinct and equally important goal alongside the achievement of mean HbA1c targets in the modern management of diabetes.

Recommendations

For Clinical Practice:

1. Clinicians should integrate an assessment of long-term HbA1c variability into the routine risk stratification for DKD. Reviewing the trend and fluctuations of HbA1c values over the preceding several years, rather than focusing solely on the most recent value, should become a standard of care.
2. The therapeutic goal for glycemic management in patients at risk for DKD should be twofold: achieving an individualized mean HbA1c target *and* promoting glycemic stability to minimize large fluctuations.
3. Greater consideration should be given to therapies known to reduce glycemic variability. The use of CGM should be expanded in high-risk patients to provide actionable data for minimizing glycemic excursions and maximizing time-in-range.

For Future Research:

1. There is a clear need for randomized controlled trials designed to test whether interventions that specifically target and reduce glycemic variability (e.g., CGM-guided therapy, specific medication classes) can slow the rate of GFR decline independently of changes in mean HbA1c.
2. Efforts should be made to standardize the measurement and reporting of long-term HbA1c variability in clinical research to facilitate future meta-analyses and the development of clinically useful risk prediction models.
3. Future studies should explore the complex interplay between glycemic variability, genetic predispositions, dietary patterns, and other lifestyle factors in determining the overall risk of DKD progression.

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