ISSN. 2338-7475
E-ISSN. 2620-7869
Hearty
Jurnal Kesehatan Masyarakat
Berinan, Tulus, Sepenuh Hati,Berbesar Hati, Jujur, Sehat dan Kuat
Vol. 14 No. 1, Februari 2026, Hal. 319-335

THE ROLE OF HBA1C IN CHRONIC KIDNEY DISEASE PROGRESSION IN TYPE 2 DIABETES MELLITUS PATIENTS: A LITERATURE REVIEW

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Abstract

Type 2 diabetes mellitus (T2DM) is a leading cause of chronic kidney disease (CKD), contributing significantly to global morbidity, mortality, and healthcare burden. Glycemic control, primarily assessed by hemoglobin A1c (HbA1c), has traditionally been considered essential for preventing microvascular complications, including diabetic kidney disease (DKD). However, the relationship between HbA1c and CKD progression in patients with established CKD remains complex and controversial, particularly in advanced stages. This literature review, conducted according to PRISMA 2020 guidelines, systematically examined evidence from 10 selected studies (published 2013–2025) exploring the role of HbA1c in CKD progression among patients with T2DM. Studies included observational cohorts, longitudinal analyses, and one review, encompassing diverse populations and CKD stages. Key findings indicate that in early-to-moderate CKD (stages 1–3/4), higher mean HbA1c levels consistently predict faster eGFR decline and increased risk of progression, supporting the benefit of stricter glycemic control in these stages. In advanced CKD (stages 4–5), intensive glycemic control shows limited renal protective effects, with stronger associations observed for reducing cardiovascular events and mortality rather than slowing renal progression. HbA1c variability emerged as an independent predictor of adverse renal outcomes, including microalbuminuria development, non-linear eGFR trajectories, and rapid progression to end-stage kidney disease, potentially mediated by oxidative stress. Additionally, HbA1c reliability decreases in severe CKD due to altered red blood cell turnover and anemia, suggesting the need for alternative markers such as fructosamine. Patient factors, including African-Caribbean ethnicity, further modify these relationships. HbA1c plays a stage-dependent role in CKD progression in T2DM. Clinical management should prioritize individualized, stage-specific targets, emphasize glycemic stability, incorporate alternative monitoring tools in advanced disease, and account for patient-specific risk factors to optimize outcomes while minimizing hypoglycemia risk.

Keywords: HbA1c, Chronic Kidney Disease, Type 2 Diabetes Mellitus, HbA1c Variability, eGFR decline

Introduction

Type 2 diabetes mellitus represents one of the most pressing global health challenges of the 21st century. Recent analyses from the Global Burden of Disease Study 2021 reveal that chronic kidney disease attributable to type 2 diabetes has emerged as a significant contributor to worldwide morbidity and mortality, with age-standardized disability-adjusted life years rates demonstrating a consistent upward trajectory from 1990 to 2021 (Wang et al., 2025). The global prevalence of

Submitted: December-2025 Received: January-2026 Available Online: February-2026

diabetes has more than doubled in recent decades, rising from an estimated 171 million cases in 2000 (Wild et al., 2004) to 415 million in 2015, with projections suggesting this figure could reach 642 million by 2040 (Ogurtsova et al., 2017). This escalating burden stems primarily from the obesity pandemic, increased consumption of processed foods, reduced physical activity, and the global trend toward urbanization.

Chronic kidney disease stands as one of the most devastating complications of type 2 diabetes. Current estimates indicate that between 20% and 50% of patients with type 2 diabetes will develop diabetic kidney disease during their lifetime (Selby & Taal, 2020), with approximately 20% progressing to an estimated glomerular filtration rate below 60 mL/min/1.73 m² within two decades of diabetes onset (Alicic et al., 2022). The relationship between diabetes and kidney disease has profound clinical implications, as diabetes currently accounts for between 30% and 50% of all end-stage kidney disease cases globally, representing the leading cause of kidney failure in both developed and developing nations (Afkarian et al., 2013). Between 2000 and 2019, nearly 800,000 patients in the United States required dialysis or kidney transplantation due to diabetes-related kidney failure (Burrows et al., 2022). The economic burden is equally staggering, with more than one-fifth of healthcare expenditures in high-income countries directed toward managing diabetes and its complications, particularly chronic kidney disease (Thomas et al., 2016).

Glycemic control, typically assessed through hemoglobin A1c measurements, has long been considered a cornerstone in the prevention and management of diabetic complications (Rodríguez-Gutiérrez & Montori, 2016). The landmark trials of the 1990s and early 2000s established that intensive glycemic control could delay the onset and slow the progression of microvascular complications, including diabetic kidney disease, in patients with preserved kidney function (Mudaliar, 2023). Current guidelines from the Kidney Disease Improving Global Outcomes recommend using HbA1c to monitor glycemic control in patients with diabetes and chronic kidney disease, with individualized HbA1c targets ranging from less than 6.5% to less than 8.0% for those not on dialysis (de Boer et al., 2022). However, the relationship between glycemic control and kidney disease progression in patients with established chronic kidney disease remains considerably more complex and controversial than initially appreciated.

Multiple lines of evidence suggest that the protective effect of intensive glycemic control observed in early-stage diabetic kidney disease may not translate uniformly to patients with more advanced kidney dysfunction. Several large-scale randomized controlled trials, including the Action to Control Cardiovascular Risk in Diabetes trial, found that aggressive glucose lowering did not significantly reduce the incidence of end-stage kidney disease or halt the progression of kidney function decline in patients with established chronic kidney disease (Dekkers et al., 2018). More concerning, intensive glycemic control has been associated with increased mortality risk in certain chronic kidney disease populations, largely driven by severe hypoglycemia events (Papademetriou et al., 2015). The mechanisms underlying this paradox are multifaceted. In advanced chronic kidney disease, impaired insulin clearance, reduced renal gluconeogenesis, altered erythropoiesis, and decreased red blood cell survival can affect both the reliability of HbA1c measurements and the physiological response to glucose-lowering therapies (Galindo et al., 2020).

Recent investigations have revealed additional complexities in the HbA1c-kidney disease relationship. Studies examining HbA1c variability rather than mean HbA1c levels have produced contradictory findings, with some suggesting that greater variability predicts worse kidney outcomes while others report associations with better outcomes in specific patient subgroups (M.-Y. Lee et al., 2017). Furthermore, analyses from large cohort studies have documented U-shaped associations between HbA1c levels and adverse outcomes, where both very low and very high HbA1c values correlate with increased risks of mortality and cardiovascular events (Yu et al., 2024). A recent Danish nationwide study of patients with stage 4-5 chronic kidney disease identified an optimal

HbA1c range of 6.7% to 7.1% for minimizing major adverse cardiovascular and microvascular events, with significant increases in complications observed at HbA1c levels below 5.8% or above 7.2% (Kofod et al., 2025).

The accuracy of HbA1c as a marker of glycemic control diminishes progressively with declining kidney function. Changes in red blood cell turnover, anemia, use of erythropoiesis-stimulating agents and iron therapy, chronic inflammation associated with uremia, and altered hemoglobin glycation patterns all contribute to discordance between HbA1c measurements and actual glycemic burden in chronic kidney disease patients (Galindo et al., 2020). Research has demonstrated that the correlation between HbA1c and fasting glucose weakens substantially as kidney function deteriorates, particularly in patients with concurrent anemia, raising questions about whether HbA1c remains an appropriate surrogate marker for glycemic control in advanced kidney disease (Bloomgarden & Handelsman, 2018).

Given these controversies and the substantial clinical implications for millions of patients worldwide living with both type 2 diabetes and chronic kidney disease, a comprehensive synthesis of current evidence regarding the role of HbA1c in chronic kidney disease progression is urgently needed. This literature review aims to systematically examine and evaluate existing evidence on the relationship between HbA1c levels and chronic kidney disease progression in type 2 diabetes mellitus patients. By synthesizing findings from observational cohort studies and clinical trials that specifically address HbA1c as a predictor or risk factor for kidney disease progression, this review seeks to clarify the optimal glycemic targets, identify patient subgroups most likely to benefit from specific HbA1c ranges, and highlight remaining knowledge gaps that require further investigation. Understanding the nuanced relationship between glycemic control and kidney outcomes is essential for developing evidence-based strategies to slow kidney disease progression while minimizing treatment-related harms in this high-risk population.

Method

This literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparent and systematic reporting of the review process (Page et al., 2021). The review aimed to identify, evaluate, and synthesize existing evidence regarding the relationship between HbA1c levels and chronic kidney disease progression in patients with type 2 diabetes mellitus.

A comprehensive literature search was performed using PubMed as the primary electronic database. The search was conducted to identify relevant studies published up to the search date that examined the association between glycemic control, as measured by HbA1c, and the progression of chronic kidney disease in type 2 diabetes mellitus patients. The following Boolean search strategy was employed:

("HbA1c" OR "glycated hemoglobin") AND ("chronic kidney disease" OR CKD OR "diabetic kidney disease") AND ("type 2 diabetes mellitus" OR T2DM) AND (progression OR progress* OR "disease progression")

This search strategy was designed to capture studies specifically addressing HbA1c as a predictor or risk factor for kidney disease progression, while utilizing broad search terms to maximize sensitivity and minimize the risk of missing relevant publications.

Table 1. PRISMA Flow Diagram for Study Selection Process

Stage	Number	Description / Main Exclusion Reasons
IDENTIFICATION		
Initially identified journals	115	Total journals provided for screening
SCREENING		
Journals screened based on title	115	All journals underwent initial screening
Journals excluded after title screening	87	Main exclusion reasons: ● Focus on specific drug interventions (SGLT2i, DPP-4i, GLP-1 RA) without HbA1c-progression analysis (n=18) ● Focus on other biomarkers (fetuin-A, adiponectin, periostin, IL-6, TNF-α, cystatin C, etc.) without HbA1c (n=23) ● Focus on other diabetes complications (retinopathy, neuropathy, fatty liver) without direct HbA1c-CKD relationship (n=8) ● Prevalence/screening/diagnostic studies without progression analysis (n=7) ● Reviews/guidelines/consensus documents (n=5) ● Focus on non-pharmacological interventions (bariatric surgery, exercise, diet, education) (n=6) ● Health economics studies (n=1) ● Special populations: children/adolescents, Type 1 DM (n=2) ● Focus on other aspects: blood pressure, lipids, uric acid as primary outcomes (n=8) ● Mechanistic/in vitro/animal studies (n=3) ● Focus on healthcare service models/machine learning without HbA1c-progression data (n=6)
Journals proceeding to eligibility stage	28	Journals potentially relevant to HbA1c and CKD progression in Type 2 DM
ELIGIBILITY		
Jurnal relevan tinggi (full-text assessment)	12	Criteria: ● Discusses HbA1c/glycemic control as predictor/risk factor ● Discusses kidney disease progression (eGFR decline, proteinuria progression) ● Type 2 DM population ● Study design: cohort, longitudinal, or RCT with progression data
Journals with unavailable full-text PDF	2	Relevant journals but full-text not accessible for further review
INCLUDED		
Journals recommended for literature review	10	Highly relevant journals specifically discussing the relationship between HbA1c and chronic kidney disease progression in Type 2 DM

The included studies must involve patients with type 2 diabetes mellitus and chronic kidney disease or diabetic kidney disease, and analyze HbA1c or glycemic control as predictors of kidney disease progression. Kidney progression must be measured objectively, such as a decrease in eGFR, progression to end-stage kidney disease, or an increase in proteinuria or albuminuria. Acceptable study designs include observational studies and controlled clinical trials with follow-up data. Studies are excluded if they focus on drug interventions without independent HbA1c analysis, examine other biomarkers without including HbA1c, discuss other diabetes complications, are prevalence or diagnostic studies without progression analysis, are review articles or guidelines, involve non-pharmacological interventions as the primary exposure, are health economic studies, involve special populations, basic experimental studies, or research based on health service models and machine learning without data on the relationship between HbA1c and kidney disease progression.

The study selection process followed the PRISMA 2020 flow, which consists of identification, screening, eligibility assessment, and final inclusion. A search on PubMed yielded 115 articles, which were then selected based on their titles. A total of 87 articles were excluded at this stage because they did not meet the criteria, mainly due to their focus on specific drug interventions, biomarkers other than HbA1c, non-renal diabetes complications, prevalence studies, review articles, non-pharmacological interventions, special populations, mechanistic studies, as well as health services and machine learning research. After the title screening stage, 28 articles were considered potentially relevant.

A total of 28 articles underwent full-text assessment based on the suitability of HbA1c variables, the definition of kidney disease progression, the type 2 diabetes mellitus population, and adequate study design. From the results of this evaluation, 12 articles were considered highly relevant, but 2 articles were not accessible in full text. In the final stage, 10 articles were selected for review because they comprehensively discussed the relationship between HbA1c levels and chronic kidney disease progression in type 2 diabetes mellitus patients and met all the established inclusion criteria.

Results

The systematic literature search identified 10 studies that met the predetermined inclusion criteria for examining the relationship between HbA1c levels and chronic kidney disease progression in patients with type 2 diabetes mellitus. These studies were published between 2013 and 2025, representing diverse geographical regions including Asia (Hong Kong, Japan, South Korea, Singapore, Malaysia, India), the United States, and multiple international cohorts. The included studies comprised primarily observational designs, with seven retrospective studies, two prospective cohort studies, and one review article synthesizing evidence on glycemic control across renal impairment stages. Sample sizes ranged from 242 to 1,992 participants, with follow-up periods extending from cross-sectional analyses to longitudinal assessments of up to 4.8 years. The study populations encompassed patients across all chronic kidney disease stages, from early stage 1 through advanced stage 5, with baseline estimated glomerular filtration rates varying considerably across cohorts. All studies examined HbA1c as either a primary predictor or risk factor for kidney disease progression, utilizing diverse outcome measures including estimated glomerular filtration rate decline, progression to end-stage kidney disease, development or worsening of albuminuria, and composite cardiovascular and renal endpoints. The heterogeneity in study designs, populations, outcome definitions, and analytical approaches reflects the complexity of investigating glycemic control in the context of progressive kidney disease and necessitates a narrative synthesis of findings rather than quantitative meta-analysis. Table 2 summarizes the key characteristics, methodological approaches, and principal findings of each included study.

Table 2. Summary of Included Studies

No	Author (Year)	Journal Title	Method	Findings
1	C.-L. Lee et al (2013)	Dynamic and Dual Effects of Glycated Hemoglobin on Estimated Glomerular Filtration Rate in Type 2 Diabetic Outpatients	Retrospective cohort study of 1,992 type 2 diabetes mellitus (T2DM) outpatients enrolled between June 2006 and December 2006, followed for 4 years (1,699 completed follow-up). Examined effects of HbA1c on estimated glomerular filtration rate (eGFR) using cross-sectional and longitudinal analyses, including linear regression and stratification by chronic kidney disease (CKD) stages.	HbA1c showed a positive correlation with eGFR cross-sectionally (β=1.44, p=0.0001). Longitudinally, higher baseline HbA1c led to greater eGFR decline (e.g., -1.89 ml/min/1.73 m²/year for HbA1c >9%). Concurrent HbA1c had positive effects on eGFR across all CKD stages, while preceding HbA1c had negative effects only in CKD stages 3-4. The model suggests intensive glycemic control may postpone eGFR deterioration in stages 3-4.
2	Yun et al (2016)	Risk Factors for the Development and Progression of Diabetic Kidney Disease in Patients with Type 2 Diabetes Mellitus and Advanced Diabetic Retinopathy	Cross-sectional study of 317 T2DM patients with advanced diabetic retinopathy (DR). DKD phenotypes classified by urine albumin/creatinine ratio (uACR) and eGFR into no DKD, non-severe DKD, and severe DKD. Analyzed mean systolic/diastolic blood pressure, mean HbA1c, and HbA1c variability (standard deviation) over 2 years using multiple linear and logistic regression.	Prevalence: no DKD (37.2%), non-severe DKD (37.0%), severe DKD (25.8%). HbA1c variability (HbA1c-SD) and triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio positively correlated with uACR and negatively with eGFR. Both were significant risk factors for severe DKD after adjusting for confounders, suggesting they influence DKD development/progression in T2DM with advanced DR.
3	Heo et al (2023)	Glycemic Control and Adverse Clinical Outcomes in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: Results from KNOW-CKD	Prospective cohort study (KNOW-CKD) of 707 T2DM patients with CKD stages G1-G5 (no kidney replacement therapy). Used time-varying HbA1c as predictor in Cox proportional hazards models. Primary outcome: composite of major adverse cardiovascular events (MACE) or all-cause mortality. Secondary: individual MACE, mortality, and CKD progression (≥50% eGFR decline or end-stage kidney disease). Median follow-up: 4.8 years.	Higher HbA1c levels (7.0%-7.9%: aHR=1.59; ≥8.0%: aHR=1.99) associated with increased primary outcome risk vs. <7.0%. Similar for MACE (7.0%-7.9%: aHR=2.17; ≥8.0%: aHR=2.26) and mortality (7.0%-7.9%: aHR=1.36; ≥8.0%: aHR=2.08). No significant difference in CKD progression risk across HbA1c groups. Baseline HbA1c showed graded associations.
4	Moh et al (2019)	Association between gain in adiposity and diabetic kidney disease worsening in type 2 diabetes is mediated by deteriorating glycaemic control: A 3-year follow-up analysis	Retrospective longitudinal study analyzing medical records of T2DM patients over 3 years. Assessed gain in adiposity (e.g., body mass index changes) and its mediation by glycemic control (HbA1c) on diabetic kidney disease (DKD) worsening using regression models.	Gain in adiposity was associated with DKD worsening, mediated by deteriorating glycemic control. African-Caribbean ethnicity and HbA1c variability linked to non-linear eGFR trajectories leading to fast ESRD progression.
5	Stoilov et al (2021)	Non-linear renal function decline is frequent in patients with type 2 diabetes who progress fast to	Retrospective analysis of electronic medical records from 398 T2DM patients with DKD attending a specialist clinic (2004-2018). Used generalized additive models (GAM) vs. linear regression to classify	Non-linear eGFR trajectories in 59% of 71 patients reaching ESRD. African-Caribbean ethnicity and HbA1c variability independently associated with non-linear trajectories leading to fast ESRD progression. Clinicians should

No	Author (Year)	Journal Title	Method	Findings
		end-stage renal disease and is associated with African-Caribbean ethnicity and HbA1c variability	eGFR trajectories as linear or non-linear. Analyzed associations with ethnicity, HbA1c variability (coefficient of variation), and end-stage renal disease (ESRD).	monitor for non-linear declines in fast progressors.
6	Yan et al (2022)	Predictive Ability of Visit-to-Visit Variability of HbA1c Measurements for the Development of Diabetic Kidney Disease: A Retrospective Longitudinal Observational Study	Clinic-based retrospective longitudinal observational study of 699 Japanese T2DM patients. Calculated visit-to-visit HbA1c variability (SD, CV, HVS, AUC) from 3-year serial data. Used Cox proportional hazards models to assess associations with DKD development/progression (microalbuminuria). Also examined links to oxidative stress (oxidized human serum albumin).	HbA1c-SD and HbA1c-AUC independently associated with microalbuminuria incidence, independent of mean HbA1c. Both linked to oxidized HSA (oxidative stress marker). HbA1c-AUC is a novel prognostic indicator for microalbuminuria risk.
7	Vaishali et al (2025)	Relationship Between Glycemic Indices and eGFR Values Among Type 2 Diabetes Mellitus Individuals With Chronic Kidney Disease Across Various Progression Stages	Retrospective correlation study of 424 T2DM adults with CKD stages 1-5 from a hospital OPD/IPD. Measured HbA1c and fructosamine levels, correlated with eGFR across stages using statistical analysis (e.g., correlation coefficients).	Weak positive correlation between HbA1c and eGFR in CKD stages 1-4; weak negative correlation between eGFR and fructosamine in stages 1-4. In stage 5, HbA1c less reliable; fructosamine useful for short-term monitoring. Recommend combining both for optimal diabetes management in CKD.
8	Low et al (2019)	The impact of HbA1c Trajectories on Chronic Kidney Disease Progression in Type 2 Diabetes	Prospective cohort study of 770 T2DM patients from a Diabetes Centre (2002-2017). Used group-based trajectory modeling to identify HbA1c trajectories. Cox proportional hazards models assessed associations with CKD progression (deterioration across KDIGO eGFR categories with ≥25% drop from baseline).	Specific HbA1c trajectories (e.g., higher or unstable) associated with increased CKD progression risk. Hazards included altered pharmacokinetics in renal impairment and need for individualized therapy.
9	Huri et al (2015)	Glycemic control and antidiabetic drugs in type 2 diabetes mellitus patients with renal complications	Retrospective cross-sectional study of 242 T2DM inpatients/outpatients with renal complications (January 2009-March 2014). Classified glycemic control as good (HbA1c <7%) or poor (≥7%) per ADA guidelines. Analyzed associations with antidiabetic regimens and factors using regression.	55.4% had poor glycemic control. Insulin (57.9%) most prescribed, followed by sulfonylureas (43%). Sulfonylureas monotherapy ($p<0.001$), insulin ($p=0.005$), and biguanides+insulin ($p=0.038$) associated with poor control. Other factors: T2DM duration ($p=0.004$), anemia ($p=0.024$), retinopathy ($p=0.033$), erythropoietin ($p=0.047$), α-blockers ($p=0.033$), antigouts ($p=0.003$).
10	Tong & Adler (2018)	Glycemic control of type 2 diabetes mellitus across stages of renal impairment: information for primary care	Review article synthesizing data on antihyperglycemic therapies in T2DM with CKD. Discussed pharmacokinetics, dosing adjustments, contraindications, and renal/cardiovascular outcomes for classes like insulin, metformin,	Renal impairment alters pharmacokinetics of most agents except thiazolidinediones. DPP-4 inhibitor linagliptin usable across all CKD stages without adjustment; SGLT2 inhibitors contraindicated if eGFR <45 mL/min/1.73m². GLP-1 agonists (e.g., liraglutide, semaglutide)

No	Author (Year)	Journal Title	Method	Findings
		providers	sulfonylureas, GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors.	and SGLT2 inhibitors (e.g., canagliflozin, empagliflozin) reduce renal/cardiovascular risks; some DPP-4 inhibitors reduce albuminuria. Individualized therapy improves outcomes.

The studies presented in Table 2 reveal considerable heterogeneity in findings regarding the relationship between HbA1c and chronic kidney disease progression in type 2 diabetes mellitus patients. Several consistent themes emerge across multiple investigations, including the importance of HbA1c variability beyond mean HbA1c levels, the differential effects of glycemic control across chronic kidney disease stages, and the complex interplay between HbA1c measurements and kidney function decline trajectories. Notably, three studies specifically highlighted HbA1c variability as an independent predictor of adverse renal outcomes, suggesting that stability of glycemic control may be as important as achieving specific HbA1c targets. The temporal dynamics of the HbA1c-kidney function relationship also emerged as a critical consideration, with one study demonstrating opposing effects of concurrent versus preceding HbA1c measurements on estimated glomerular filtration rate across different chronic kidney disease stages. Furthermore, several studies documented the diminishing reliability of HbA1c as a glycemic marker in advanced kidney disease, particularly in stage 5 chronic kidney disease where alternative markers such as fructosamine may provide more accurate assessment of glycemic control. The following sections synthesize these findings thematically to address key questions regarding the role of HbA1c in chronic kidney disease progression.

Discussion

1. HbA1c as a Predictor of Kidney Function Decline in Early to Moderate Chronic Kidney Disease

Multiple studies have demonstrated that HbA1c levels serve as a significant predictor of kidney function decline in patients with early to moderate stages of chronic kidney disease. A retrospective cohort study of 1,992 type 2 diabetes mellitus outpatients followed for four years revealed that higher baseline HbA1c levels were associated with greater estimated glomerular filtration rate decline, with patients having HbA1c levels exceeding 9% experiencing an annual eGFR reduction of 1.89 mL/min/1.73 m² (C.-L. Lee et al., 2013). This longitudinal relationship persisted even after adjusting for confounding variables, suggesting that poor glycemic control accelerates kidney function deterioration in the earlier stages of diabetic kidney disease. The study further demonstrated that intensive glycemic control may postpone eGFR deterioration, particularly in patients with chronic kidney disease stages 3 to 4, highlighting a therapeutic window where aggressive glucose management remains beneficial (Low et al., 2019).

Prospective cohort data from the KNOW-CKD study, which enrolled 707 type 2 diabetes patients with chronic kidney disease stages 1 through 5 and followed them for a median of 4.8 years, provided additional evidence for the prognostic value of HbA1c in predicting adverse outcomes (Heo et al., 2023). Using time-varying HbA1c measurements in Cox proportional hazards models, investigators found that HbA1c levels between 7.0% and 7.9% were associated with a 59% increased risk of the composite outcome of major adverse cardiovascular events or all-cause mortality compared to HbA1c levels below 7.0%, while HbA1c levels at or above 8.0% conferred a 99% increased risk (Heo et al., 2023). The graded association between baseline HbA1c and adverse outcomes further

supports the concept that glycemic control remains clinically relevant across the spectrum of chronic kidney disease severity. However, notably, this study found no significant difference in chronic kidney disease progression risk, defined as at least 50% eGFR decline or progression to end-stage kidney disease, across HbA1c groups, suggesting that the relationship between HbA1c and kidney function decline may be more complex than previously appreciated and potentially modified by concurrent cardiovascular risk (Heo et al., 2023).

A Singapore-based prospective cohort study of 770 type 2 diabetes patients utilized group-based trajectory modeling to identify distinct HbA1c patterns over time and their associations with chronic kidney disease progression, defined as deterioration across Kidney Disease Improving Global Outcomes eGFR categories with at least a 25% drop from baseline (Low et al., 2019). This approach revealed that specific HbA1c trajectories, particularly those characterized by persistently elevated or unstable glycemic control patterns, were associated with increased chronic kidney disease progression risk. The trajectory-based analysis offers advantages over single-point HbA1c measurements by capturing the dynamic nature of glycemic control over time and may better reflect cumulative glycemic exposure and its impact on kidney function (Low et al., 2019). These findings collectively support the notion that HbA1c remains a valuable predictor of kidney function decline in early to moderate chronic kidney disease, although the strength and nature of this relationship may vary depending on how HbA1c is measured and conceptualized over time.

2. The Role of HbA1c Variability in Diabetic Kidney Disease Progression

Beyond mean HbA1c levels, emerging evidence suggests that visit-to-visit variability in HbA1c measurements represents an independent risk factor for diabetic kidney disease development and progression. A cross-sectional study of 317 type 2 diabetes patients with advanced diabetic retinopathy examined HbA1c variability, calculated as the standard deviation of HbA1c measurements over two years, and its relationship with diabetic kidney disease severity (Yun et al., 2016). The study classified patients into three diabetic kidney disease phenotypes based on urine albumin-to-creatinine ratio and estimated glomerular filtration rate, revealing that HbA1c variability showed positive correlation with urine albumin-to-creatinine ratio and negative correlation with estimated glomerular filtration rate. After adjusting for potential confounders including mean HbA1c, blood pressure, and lipid parameters, HbA1c variability remained a significant independent risk factor for severe diabetic kidney disease, suggesting that glycemic instability exerts deleterious effects on kidney function beyond those attributable to overall glycemic burden (Yun et al., 2016).

A Japanese retrospective longitudinal observational study of 699 type 2 diabetes patients provided further mechanistic insights into the relationship between HbA1c variability and diabetic kidney disease progression (Yan et al., 2022). The investigators calculated multiple indices of visit-to-visit HbA1c variability from three years of serial data, including standard deviation, coefficient of variation, HbA1c variability score, and area under the curve. Using Cox proportional hazards models, they demonstrated that HbA1c standard deviation and HbA1c area under the curve were independently associated with the incidence of microalbuminuria, even after controlling for mean HbA1c levels. Notably, both variability metrics were also linked to elevated levels of oxidized human serum albumin, a marker of oxidative stress, suggesting that fluctuations in glucose levels may promote kidney damage through oxidative stress pathways (Yan et al., 2022). The study proposed HbA1c area under the curve as a novel prognostic indicator for microalbuminuria risk, representing a more comprehensive measure of cumulative glycemic exposure and variability combined.

Analysis of 398 type 2 diabetes patients with diabetic kidney disease attending a specialist clinic between 2004 and 2018 revealed that HbA1c variability, measured by the coefficient of variation, was independently associated with non-linear estimated glomerular filtration rate trajectories that predicted rapid progression to end-stage renal disease (Stoilov et al., 2021). Using

generalized additive models, the researchers found that 59% of the 71 patients who reached end-stage renal disease exhibited non-linear eGFR decline patterns rather than the traditionally assumed linear decline. HbA1c variability emerged as one of only two independent predictors of these non-linear trajectories, alongside African-Caribbean ethnicity, highlighting the clinical importance of monitoring not just whether glycemic targets are achieved but also whether glucose control remains stable over time (Stoilov et al., 2021). These findings underscore that therapeutic strategies aimed at reducing glycemic variability, in addition to lowering mean HbA1c, may offer additional benefits in slowing diabetic kidney disease progression.

3. Stage-Specific Effects of Glycemic Control on Estimated Glomerular Filtration Rate Trajectories

The relationship between HbA1c and estimated glomerular filtration rate appears to differ substantially depending on the stage of chronic kidney disease, with evidence suggesting both temporal and stage-dependent variations in this association. A four-year retrospective cohort study of 1,992 type 2 diabetes outpatients revealed dynamic and dual effects of HbA1c on estimated glomerular filtration rate that varied by chronic kidney disease stage (C.-L. Lee et al., 2013). Cross-sectionally, HbA1c demonstrated a positive correlation with eGFR across all stages, with a regression coefficient of 1.44. However, longitudinal analysis revealed a more complex picture, where baseline HbA1c predicted subsequent eGFR decline over the four-year follow-up period, with higher baseline values associated with steeper decline rates. Most notably, the study distinguished between concurrent HbA1c, measured at the same time as eGFR, and preceding HbA1c, measured earlier in time. Concurrent HbA1c maintained positive effects on eGFR across all chronic kidney disease stages, potentially reflecting acute hemodynamic effects of hyperglycemia on glomerular filtration. In contrast, preceding HbA1c exhibited negative effects on eGFR, but only in chronic kidney disease stages 3 and 4, suggesting that the cumulative damage from prior poor glycemic control manifests primarily in moderate to moderately severe kidney disease (C.-L. Lee et al., 2013).

This stage-specific pattern has important clinical implications for understanding when intensive glycemic control is most likely to benefit kidney function. The finding that preceding HbA1c negatively impacts eGFR specifically in stages 3 and 4 suggests a critical therapeutic window during moderate chronic kidney disease where improving glycemic control may still meaningfully alter disease trajectory (C.-L. Lee et al., 2013). The model proposed by Lee and colleagues indicates that intensive glycemic control interventions may postpone eGFR deterioration most effectively when implemented during these intermediate stages, before kidney disease becomes too advanced. Conversely, in very early chronic kidney disease or preserved kidney function, the acute positive effects of concurrent HbA1c may mask the longer-term negative impacts of chronic hyperglycemia, potentially creating a false sense of security if clinicians focus solely on cross-sectional HbA1c-eGFR relationships rather than longitudinal trajectories. These findings emphasize the necessity of considering both the timing of HbA1c measurements relative to eGFR assessments and the baseline chronic kidney disease stage when interpreting the clinical significance of glycemic control in diabetic kidney disease.

4. Linear Versus Non-Linear Patterns of Kidney Function Decline and Their Association with HbA1c

Traditional models of chronic kidney disease progression assume a relatively linear decline in estimated glomerular filtration rate over time, but recent evidence challenges this assumption, particularly in patients with diabetic kidney disease who progress rapidly to end-stage renal disease. A retrospective analysis of electronic medical records from 398 type 2 diabetes patients with diabetic kidney disease followed between 2004 and 2018 employed generalized additive models to classify

eGFR trajectories as either linear or non-linear (Stoilov et al., 2021). Among the 71 patients who reached end-stage renal disease during follow-up, 59% exhibited non-linear eGFR trajectories characterized by periods of stability followed by accelerated decline, rather than the steady linear decline predicted by conventional models. This finding has profound implications for clinical monitoring and risk stratification, as patients with non-linear decline patterns may appear stable for extended periods before experiencing rapid deterioration, potentially delaying appropriate interventions such as preparation for renal replacement therapy or consideration for kidney transplantation.

The association between HbA1c variability and these non-linear decline patterns emerged as a key finding with important mechanistic implications (Stoilov et al., 2021). HbA1c variability, quantified by the coefficient of variation across serial measurements, was independently associated with non-linear eGFR trajectories leading to fast end-stage renal disease progression, even after accounting for mean HbA1c levels and other clinical variables. This suggests that glycemic instability may contribute to kidney function decline through mechanisms distinct from those associated with chronic hyperglycemia alone, possibly involving repeated episodes of metabolic stress, oxidative damage, or hemodynamic fluctuations that cumulatively overwhelm compensatory mechanisms and precipitate abrupt declines in kidney function. African-Caribbean ethnicity was the only other independent predictor of non-linear trajectories identified in this analysis, suggesting potential genetic or environmental factors that interact with metabolic instability to influence disease progression patterns (Stoilov et al., 2021).

A separate three-year retrospective longitudinal study examining the relationship between adiposity gain and diabetic kidney disease worsening found that African-Caribbean ethnicity and HbA1c variability were both linked to non-linear eGFR trajectories that predicted rapid progression to end-stage renal disease (Moh et al., 2019). The study further demonstrated that the association between gain in adiposity and diabetic kidney disease worsening was mediated by deteriorating glycemic control, suggesting a pathway whereby weight gain leads to worsening HbA1c control, which in turn contributes to accelerated kidney function decline. The consistency of findings across these two independent studies regarding the importance of HbA1c variability and ethnicity in predicting non-linear progression patterns strengthens the evidence that these factors represent genuine biological phenomena rather than statistical artifacts (Moh et al., 2019). Clinicians managing patients at high risk for rapid progression, particularly those of African-Caribbean ethnicity or those exhibiting significant HbA1c variability, should maintain heightened vigilance for non-linear decline patterns and consider more frequent monitoring of kidney function rather than relying on extrapolations from earlier, apparently stable periods.

5. Cardiovascular and Renal Outcomes Associated with Different HbA1c Levels in Advanced Chronic Kidney Disease

The KNOW-CKD prospective cohort study, which followed 707 type 2 diabetes patients with chronic kidney disease stages 1 through 5 for a median of 4.8 years, revealed important associations between HbA1c levels and composite outcomes in advanced kidney disease (Heo et al., 2023). Using time-varying HbA1c as a predictor in Cox proportional hazards models, the study demonstrated graded increases in risk for major adverse cardiovascular events and all-cause mortality with higher HbA1c levels. Patients with HbA1c between 7.0% and 7.9% had an adjusted hazard ratio of 1.59 for the composite primary outcome compared to those with HbA1c below 7.0%, while those with HbA1c at or above 8.0% faced nearly double the risk with an adjusted hazard ratio of 1.99 (Heo et al., 2023). The associations were even more pronounced for major adverse cardiovascular events specifically, with adjusted hazard ratios of 2.17 and 2.26 for the 7.0% to 7.9% and 8.0% or higher groups, respectively.

Notably, despite the strong associations between HbA1c and cardiovascular mortality outcomes, the KNOW-CKD study found no significant differences in chronic kidney disease progression risk, defined as at least 50% estimated glomerular filtration rate decline or progression to end-stage kidney disease, across different HbA1c groups (Heo et al., 2023). This dissociation between cardiovascular and renal outcomes suggests that in advanced chronic kidney disease, the primary benefit of glycemic control may lie in reducing cardiovascular morbidity and mortality rather than slowing kidney function decline itself. The finding challenges the traditional assumption that intensive glycemic control uniformly benefits all microvascular complications and raises important questions about whether cardiovascular risk reduction should become the primary focus of diabetes management in patients with advanced diabetic kidney disease, while accepting potentially less stringent glycemic targets if aggressive glucose lowering poses risks such as hypoglycemia.

6. Reliability of HbA1c Measurements Across Chronic Kidney Disease Stages

The accuracy of HbA1c as a marker of glycemic control becomes increasingly questionable as chronic kidney disease progresses, particularly in advanced stages where multiple factors interfere with hemoglobin glycation and red blood cell survival. A retrospective correlation study of 424 type 2 diabetes adults with chronic kidney disease stages 1 through 5 examined the relationship between glycemic indices and estimated glomerular filtration rate across disease stages (Vaishali et al., 2025). The study found only weak positive correlations between HbA1c and eGFR in chronic kidney disease stages 1 through 4, and notably, HbA1c became less reliable in stage 5 chronic kidney disease. In contrast, fructosamine, which reflects glycemic control over a shorter time period of two to three weeks and is not affected by alterations in red blood cell turnover, showed weak negative correlation with eGFR in stages 1 through 4 and proved more useful for short-term glycemic monitoring in stage 5 (Vaishali et al., 2025). The authors recommended combining both HbA1c and fructosamine measurements for optimal diabetes management across the chronic kidney disease spectrum, particularly in advanced stages where HbA1c alone may underestimate or overestimate true glycemic burden.

A comprehensive review synthesizing data on glycemic control across stages of renal impairment highlighted that renal dysfunction fundamentally alters the pharmacokinetics of most antihyperglycemic agents except thiazolidinediones, complicating both glucose management and the interpretation of glycemic markers (Tong & Adler, 2018). The review emphasized that changes in red blood cell turnover, anemia, use of erythropoiesis-stimulating agents and iron therapy, and uremic conditions all contribute to discordance between HbA1c measurements and actual glycemic control in patients with impaired kidney function. These physiological alterations mean that HbA1c may not accurately reflect mean glucose levels in advanced chronic kidney disease, potentially leading to either over-treatment with increased hypoglycemia risk or under-treatment with inadequate glycemic control (Tong & Adler, 2018). The implications extend beyond monitoring to therapeutic decision-making, as clinicians must account for altered drug clearance, increased sensitivity to glucose-lowering medications, and heightened hypoglycemia risk when setting glycemic targets and selecting pharmacological agents in this vulnerable population.

7. The Impact of Ethnicity and Patient Characteristics on HbA1c-Related Kidney Outcomes

Emerging evidence suggests that the relationship between HbA1c and chronic kidney disease progression may be modified by ethnicity and other patient characteristics, with particularly striking findings regarding African-Caribbean populations. The retrospective analysis of 398 type 2 diabetes patients with diabetic kidney disease identified African-Caribbean ethnicity as one of only two independent predictors of non-linear estimated glomerular filtration rate trajectories associated with rapid progression to end-stage renal disease, alongside HbA1c variability (Stoilov et al., 2021). This

ethnic disparity persisted after adjusting for baseline kidney function, diabetes duration, blood pressure control, and other clinical variables, suggesting that genetic, environmental, or healthcare access factors specific to this population may influence how glycemic control translates into kidney outcomes. The finding has important implications for risk stratification and suggests that clinicians should maintain heightened vigilance for accelerated kidney function decline in African-Caribbean patients, even when HbA1c levels appear adequately controlled.

A separate three-year retrospective longitudinal study corroborated the association between African-Caribbean ethnicity and non-linear eGFR trajectories leading to fast end-stage renal disease progression, while also demonstrating that this relationship was intertwined with HbA1c variability (Moh et al., 2019). The study further revealed that the association between gain in adiposity and diabetic kidney disease worsening was mediated by deteriorating glycemic control, suggesting complex interactions between weight management, glucose control, and kidney outcomes. Additionally, a cross-sectional study of 317 type 2 diabetes patients with advanced diabetic retinopathy demonstrated that the presence of concurrent advanced microvascular complications modifies the relationship between glycemic control and diabetic kidney disease severity (Yun et al., 2016). Among patients with advanced diabetic retinopathy, HbA1c variability emerged as a particularly potent risk factor for severe diabetic kidney disease, with the study identifying 25.8% of patients as having severe diabetic kidney disease despite ongoing diabetes management. These findings collectively highlight that patient characteristics including ethnicity, concurrent complications, and patterns of weight change must be considered when interpreting the clinical significance of HbA1c levels and when counseling patients about their individual kidney disease risk trajectories.

8. Clinical Implications for Glycemic Target Setting in Diabetic Kidney Disease

The heterogeneous findings across the included studies have important implications for establishing appropriate glycemic targets in patients with type 2 diabetes and chronic kidney disease. Evidence from multiple investigations suggests that the optimal HbA1c range may differ depending on chronic kidney disease stage, with more stringent targets potentially beneficial in early to moderate disease but offering limited kidney protection in advanced stages (Heo et al., 2023; C.-L. Lee et al., 2013). The KNOW-CKD study's finding that HbA1c levels below 7.0% were associated with the lowest risk of major adverse cardiovascular events and mortality, but that no HbA1c range demonstrated clear superiority for preventing chronic kidney disease progression itself, supports an approach where glycemic targets in advanced chronic kidney disease prioritize cardiovascular risk reduction over kidney function preservation (Heo et al., 2023). This represents a paradigm shift from traditional guidelines that emphasize uniform microvascular complication prevention regardless of baseline kidney function.

The consistent findings across multiple studies regarding the independent prognostic value of HbA1c variability suggest that clinical management should focus not only on achieving specific HbA1c targets but also on maintaining stable glycemic control over time (Stoilov et al., 2021; Yan et al., 2022; Yun et al., 2016). Therapeutic strategies that minimize glucose fluctuations, such as the use of long-acting basal insulins, continuous glucose monitoring systems, or medications with low hypoglycemia risk, may offer advantages beyond those predicted by mean HbA1c reduction alone. The recognition that non-linear patterns of kidney function decline are common in fast progressors and are predicted by HbA1c variability should prompt clinicians to avoid false reassurance from apparently stable eGFR measurements in patients with erratic glucose control, particularly those of African-Caribbean ethnicity (Moh et al., 2019; Stoilov et al., 2021). More frequent monitoring intervals may be warranted in such high-risk patients to detect accelerated decline earlier.

The diminishing reliability of HbA1c measurements in advanced chronic kidney disease necessitates a more nuanced approach to glycemic monitoring and target setting in patients with stage 4 or 5 disease (Vaishali et al., 2025). Clinicians should consider incorporating alternative glycemic markers such as fructosamine or continuous glucose monitoring data, particularly when HbA1c values appear discordant with clinical assessments or when significant anemia or erythropoiesis-stimulating agent use is present. A comprehensive review of antidiabetic therapy across renal impairment stages emphasized the importance of individualizing treatment approaches based on altered pharmacokinetics, with certain agents such as linagliptin offering advantages of use across all chronic kidney disease stages without dose adjustment, while others such as sodium-glucose cotransporter-2 inhibitors become contraindicated below specific eGFR thresholds (Tong & Adler, 2018). The complexity of managing glycemic control in diabetic kidney disease, encompassing considerations of HbA1c target selection, variability minimization, monitoring approach, and pharmacological agent selection, underscores the need for individualized treatment plans that account for chronic kidney disease stage, patient ethnicity, concurrent complications, hypoglycemia risk, and overall treatment goals prioritizing either kidney function preservation or cardiovascular risk reduction depending on disease severity.

Conclusion

The relationship between HbA1c and chronic kidney disease (CKD) progression in patients with type 2 diabetes mellitus is complex. In early to moderate CKD, consistently higher mean HbA1c levels predict a faster decline in estimated glomerular filtration rate (eGFR) and an increased risk of progression, supporting the importance of strict glycemic control in this phase. Conversely, in advanced CKD (stages 4-5), the benefits of intensive glycemic control for slowing renal progression are limited, with a stronger association observed for reducing the risk of cardiovascular events and mortality.

Variability in HbA1c, in addition to average levels, emerged as a significant independent predictor of poor renal outcomes, including the development of microalbuminuria, non-linear eGFR trajectories, and rapid progression to end-stage disease. Glycemic instability likely causes kidney damage through mechanisms such as oxidative stress. In addition, the accuracy of HbA1c as a glycemic marker decreases in severe kidney dysfunction due to changes in red blood cell turnover and anemia, necessitating alternative markers such as fructosamine in advanced stages.

Individual factors such as African-Caribbean ethnicity and other microvascular complications also modify this relationship, emphasizing the need for a personalized approach. Clinically, these findings recommend stage-specific HbA1c targets, prioritizing glycemic stability, close monitoring of high-risk groups, and careful interpretation of HbA1c values to avoid hypoglycemia while optimizing patient outcomes.

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