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GLYCATION GAP AND HEMOGLOBIN GLYCATION INDEX IN TYPE 2 DIABETIC KIDNEY DISEASE: PATHOPHYSIOLOGICAL BASIS, CLINICAL EVIDENCE AND FUTURE PERSPECTIVES

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ABSTRACT

Objective: To synthesize the pathophysiological basis, methods of determination and clinical evidence for the glycation gap (GG) and the hemoglobin glycation index (HGI) in type 2 diabetic kidney disease. **Methods:** A structured narrative review. PubMed/MEDLINE, the Cochrane Library, Google Scholar and the official American Diabetes Association and KDIGO websites were searched up to 31 July 2026, with predefined inclusion and exclusion criteria and an author-assigned risk-of-bias rating for each study. **Results:** GG and HGI are residual indices, calculated as measured HbA1c minus HbA1c predicted from fructosamine or from glucose. Both may reflect the combined influence of several biological and measurement-related sources of variation rather than hemoglobin glycation alone, and both depend on a population-specific regression equation, so values are not directly comparable across studies. Cross-sectional studies report associations of a higher GG or HGI with albuminuria and prevalent kidney disease. In type 2 diabetes, a 5-year cohort found a 58% higher risk of renal progression in the highest tertile of first-year mean HGI (HR 1.58; 95% CI 1.01-2.49), whereas a 1,050-patient cohort described a U-shaped association with incident nephropathy. Incremental predictive value beyond HbA1c, the urinary albumin-to-creatinine ratio and estimated glomerular filtration rate has not been established. Anemia, altered erythrocyte turnover, erythropoiesis-stimulating therapy, hypoalbuminemia and proteinuria may all bias the indices. **Conclusion:** GG and HGI may help interpret an HbA1c value that is discordant with directly measured glucose. Current evidence does not support their independent use for diagnosis, renal risk stratification or adjustment of treatment.

Keywords: glycation gap; hemoglobin glycation index; diabetic kidney disease; HbA1c; albuminuria.
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1. INTRODUCTION

HbA1c is the central marker for assessing long-term glycemic control and for setting treatment targets in people with diabetes. Its value, however, is determined by far more than glucose alone: erythrocyte lifespan, the rate of red cell production and destruction, glucose permeability across the red cell membrane, hemoglobin structure and several other biological factors all contribute. Consequently, two people with comparable mean glucose may have different HbA1c values, and an identical HbA1c does not guarantee identical glucose exposure [1-3]. This discordance is particularly important in diabetic chronic kidney disease. As kidney disease progresses, anemia, iron deficiency, transfusion, erythropoiesis-stimulating therapy, chronic inflammation, metabolic acidosis and dialysis can all reduce the reliability of HbA1c. Glycated protein markers such as fructosamine or glycated albumin reflect a shorter time window, but are themselves affected by hypoalbuminemia, proteinuria, malnutrition and altered albumin turnover. KDIGO therefore continues to regard HbA1c as the foundational marker while recommending directly measured glucose or continuous glucose monitoring whenever HbA1c is inconsistent with the clinical picture [2,4]. The glycation gap (GG) and the hemoglobin glycation index (HGI) were developed to quantify the difference between observed HbA1c and HbA1c predicted from another glucose marker. GG uses fructosamine as the predictor, whereas HGI is usually derived from fasting plasma glucose or mean glucose. Both concepts point towards an individual "glycation phenotype", yet they differ in the comparator used, the time window reflected and the confounders involved [5-7]. Early studies showed that a positive GG accompanied diabetic kidney disease, while more recent reports have linked a high HGI, or an HGI far from the center of its distribution, with albuminuria and a declining glomerular filtration rate. The statistical independence of these indices from HbA1c, their standardization across populations and their added value in practice all remain under debate. This review brings together the pathophysiological basis, methods of calculation, clinical evidence and limitations of GG and HGI in type 2 diabetic kidney disease, and identifies research gaps relevant to the Vietnamese setting.

2. REVIEW METHODS

This article was prepared as a structured narrative review. The literature was searched in PubMed/MEDLINE, the Cochrane Library, Google Scholar, the official websites of the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO), and reputable Vietnamese medical journals. The last search date was 31 July 2026. The search string combined MeSH terms with free-text keywords as follows: ("glycation gap" OR "glycosylation gap" OR "hemoglobin glycation index" OR "HbA1c discordance") AND ("diabetic nephropathies"[MeSH] OR "diabetic kidney disease" OR albuminuria OR "glomerular filtration rate" OR "renal progression") AND ("diabetes mellitus, type 2"[MeSH] OR "type 2 diabetes"). Supplementary keywords were fructosamine, "glycated albumin", "continuous glucose monitoring" and "glucose management indicator". The corresponding Vietnamese search terms were "khoảng trống glycat hóa", "chỉ số glycat hóa hemoglobin", "bệnh thận đái tháo đường" and "đạm niệu".

Studies were eligible if they were conducted in adults, calculated or reported GG, HGI or the difference between HbA1c and the glucose management indicator, reported at least one renal outcome (albuminuria, estimated glomerular filtration rate or progression of kidney disease), and were published in English or Vietnamese. Practice guidelines, mechanistic reviews and studies of assay methodology were included separately to support the section on physiological basis. Exclusion criteria were case reports, conference abstracts, documents without full text, and studies reporting only non-renal outcomes. Publications from 2010 to 2026 were prioritized; earlier work was retained only where necessary to describe the origin of the concepts.

Screening of titles, then abstracts and finally full texts was performed by the corresponding author and reviewed by the whole group. Extracted data comprised study design, population, type of diabetes, baseline kidney status, method of calculating the index and the source of the regression equation, outcomes, effect

estimates and the variables adjusted for. Table 2 presents studies selected according to three criteria: a clearly defined renal outcome, sufficient information on design and index calculation, and representation of different designs and populations; it is not an exhaustive list of all publications on the topic. Statements made in this review are stratified by study design. Cross-sectional studies permit conclusions only about associations with albuminuria or prevalent kidney disease; only cohort studies allow discussion of the ability to predict a decline in glomerular filtration rate or renal events. Evidence derived from type 1 diabetes or from mixed populations is presented separately, as the basis on which these concepts were formed, and is not extrapolated directly to type 2 diabetes.

3. REVIEW

3.1. PHYSIOLOGICAL BASIS OF GLYCATION MARKERS

3.1.1. The glycation reaction and the formation of advanced glycation end products

Glycation is a non-enzymatic reaction between the carbonyl group of a reducing sugar and a free amino group of a protein, lipid or nucleic acid. The early stage generates an unstable Schiff base that is subsequently converted into an Amadori product; through oxidation, dehydration, rearrangement and cross-linking, these structures progress to advanced glycation end products (AGEs). The reaction rate varies with glucose concentration, duration of exposure, the degree of oxidative stress, antioxidant capacity and the turnover rate of the target molecule [8].

AGEs directly alter the structure and function of extracellular matrix proteins and activate the RAGE receptor on endothelial cells, mesangial cells, podocytes and renal tubular epithelial cells. The AGEs-RAGE axis promotes the generation of reactive oxygen species, activates NF-κB and increases the expression of inflammatory cytokines, TGF-β and profibrotic factors. The result is endothelial dysfunction, thickening of the glomerular basement membrane, mesangial expansion, podocyte foot process effacement, increased albumin permeability and renal fibrosis. These mechanisms suggest that the degree of glycation within tissue may carry information about renal injury beyond that provided by a single glucose measurement. This remains an inference from mechanistic research; to date there is no data directly demonstrating that GG or HGI measured in clinical practice accurately reflects the glycation burden within renal tissue [8].

3.1.2. HbA1c: intracellular glycation and sources of biological variation

HbA1c is formed within erythrocytes through the glycation of hemoglobin and reflects glucose exposure over most of the red cell lifespan. Because young and old erythrocytes contribute unequally, HbA1c is influenced more strongly by glucose levels in the weeks immediately preceding the test. Beyond glucose, HbA1c also depends on mean erythrocyte age, the rate of erythropoiesis, blood loss, hemolysis, iron deficiency, hemoglobinopathies, transfusion, pregnancy, erythropoiesis-stimulating agents and kidney function [1-3].

The observation that individuals show fairly stable differences in HbA1c at the same glucose level gave rise to the hypothesis of “high glycator” and “low glycator” phenotypes. Proposed mechanisms include differences in erythrocyte survival, the plasma-to-erythrocyte glucose gradient, transmembrane glucose transport, deglycating systems such as fructosamine-3-kinase, genetic factors and inflammatory status. The relative contribution of each mechanism remains incompletely defined and may vary between populations. The term glycation phenotype is also only one of several possible interpretations: the differences observed may equally arise from the mismatch in time windows between markers, from glucose variability not captured by the predictor variable, and from assay error [3,6,9].

3.1.3. Fructosamine and glycated albumin: extracellular glycation

Fructosamine is the collective term for glycated serum proteins, of which albumin accounts for the largest share owing to its high plasma concentration. Because serum proteins have a shorter half-life than erythrocytes, fructosamine and glycated albumin reflect mean glucose over approximately 2-3 weeks, which is useful when an early treatment response must be assessed or when HbA1c is confounded by red cell

abnormalities. In return, these markers vary with albumin concentration, inflammation, liver disease, thyroid disorders, protein loss through the kidney or gastrointestinal tract, and the rate of protein catabolism [4].

In diabetic kidney disease, proteinuria and hypoalbuminemia shorten albumin residence time, so that fructosamine or glycated albumin falls below the level corresponding to true glucose exposure. In chronic kidney disease, therefore, extracellular markers are not necessarily more accurate than HbA1c; test selection must be based on the dominant source of bias in the individual patient [2,4].

3.2. DEFINITION, CALCULATION AND INTERPRETATION OF GG AND HGI

3.2.1. The glycation gap

Cohen et al. defined GG as the difference between measured HbA1c and HbA1c predicted from fructosamine within the same population: GG = observed HbA1c - HbA1c predicted from fructosamine. A positive GG indicates hemoglobin glycation higher than predicted from the glycation of serum proteins, and a negative GG indicates the converse. The original study found that GG had a wide distribution and correlated closely between two measurements taken 23 ± 2 weeks apart (r = 0.81), suggesting a relatively stable biological component [5].

The regression equation used to predict HbA1c must be derived from the study population itself or from an appropriate reference population. An alternative approach converts fructosamine into a standardized deviation score and then maps it onto the HbA1c distribution, to reduce the mathematical dependence between predicted and observed HbA1c [9]. Whichever method is used, GG remains a derived index rather than a directly measured laboratory value, and there is still no internationally agreed standard for “negative”, “intermediate” or “positive” thresholds.

3.2.2. The hemoglobin glycation index

HGI is likewise calculated as observed HbA1c minus predicted HbA1c, the difference being that the predicted value is usually derived from fasting plasma glucose, from mean glucose across several measurements, or from mean glucose obtained by continuous monitoring. A positive HGI indicates an HbA1c higher than expected at the corresponding glucose level, and a negative HGI the opposite. Because the glucose-HbA1c equation varies with age, ethnicity, assay method, treatment regimen and the distribution of glucose values, HGI values from two studies that used different equations cannot be compared directly [6,7,9].

An HGI calculated from a single fasting glucose value is readily influenced by day-to-day variability, the dawn phenomenon and the difference between fasting and postprandial glucose. An HGI based on multiple measurements or on CGM is physiologically more appropriate, yet it is still not equivalent to GG, because fructosamine and directly measured glucose reflect different time windows and different biological compartments. A study of 36 patients with type 2 diabetes who underwent CGM showed that GG (calculated from glycated albumin) and HGI were both reproducible and closely correlated with each other, although the two indices were not entirely concordant [7]. In essence, both GG and HGI are residual indices that may reflect the combined influence of interindividual differences in hemoglobin glycation, erythrocyte lifespan, glucose exposure not fully captured by the predictor variable, serum protein kinetics and measurement error. Because a residual is always calculated relative to a regression line estimated from the study population itself, the absolute value of GG or HGI carries no meaning independent of that population and cannot be compared directly across studies using different equations. Geometrically, both are the residual of measured HbA1c relative to the regression line, differing only in the predictor variable plotted on the horizontal axis (Figure 1).

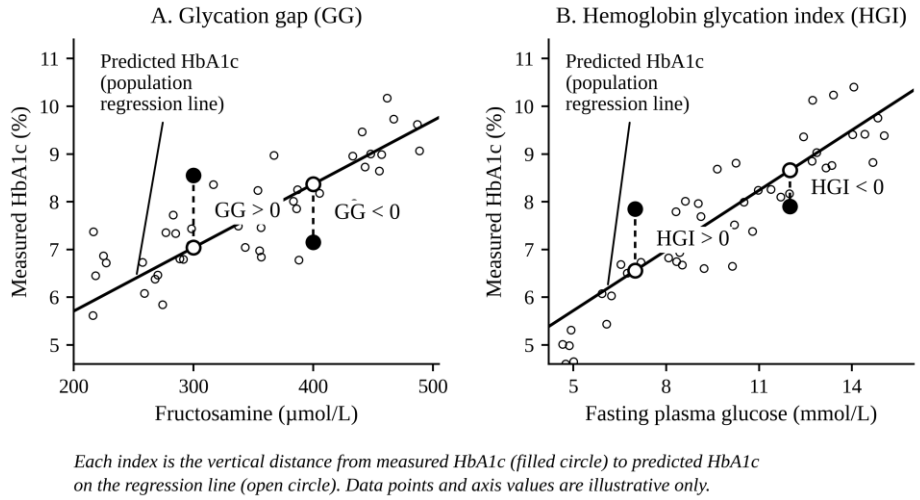


Figure 1. The glycation gap and the hemoglobin glycation index are expressed as residuals from the population regression line [5,7-9]

Table 1. Comparison of glucose markers and glycation discordance indices

Marker	Basis / method of determination	Period reflected	Main advantages	Main limitations in chronic kidney disease
HbA1c	Proportion of hemoglobin glycated within erythrocytes	Approximately 8-12 weeks	Well standardized; strong outcome evidence; widely available assay	Reduced reliability in anemia, hemolysis, transfusion, erythropoietin use, dialysis or hemoglobinopathy
Fructosamine	Total glycated serum proteins, mainly albumin	Approximately 2-3 weeks	Independence of erythrocyte lifespan; reflects early change	Affected by serum albumin, proteinuria, liver disease, inflammation and protein turnover
Glycated albumin	Proportion of albumin that is glycated, relative to total albumin	Approximately 2-3 weeks	More specific than fructosamine with respect to albumin	Biased by hypoalbuminemia, nephrotic syndrome, peritoneal dialysis and thyroid disorders
GG	Measured HbA1c minus HbA1c predicted from fructosamine or glycated albumin	Does not correspond to a defined time period; it is the residual between two markers with different time windows	Quantifies the degree of discordance between HbA1c and glycated proteins; may help explain situations in which the two markers disagree	Depends on the population-specific equation and is therefore not directly comparable across studies; subject to bias in both HbA1c and glycated proteins; no standard threshold
HGI	Measured HbA1c minus HbA1c predicted from fasting or mean glucose	Does not correspond to a defined time; it is the residual between HbA1c, and the value predicted from glucose	Can be calculated from routine tests; supported by extensive outcome data	Depends on the type of glucose measurement and on the equation used; mathematically correlated with HbA1c; not standardized across studies and therefore not directly comparable
GMI	HbA1c estimated from mean glucose obtained by CGM	The CGM wear period, usually 10-14 days or longer	Direct measurement of glucose exposure; detects variability and hypoglycemia	Cost, accessibility, minimum data requirements and sensor accuracy; GMI is not a measured HbA1c

Note: CGM: continuous glucose monitoring; GG: glycation gap; GMI: glucose management indicator; HGI: hemoglobin glycation index.

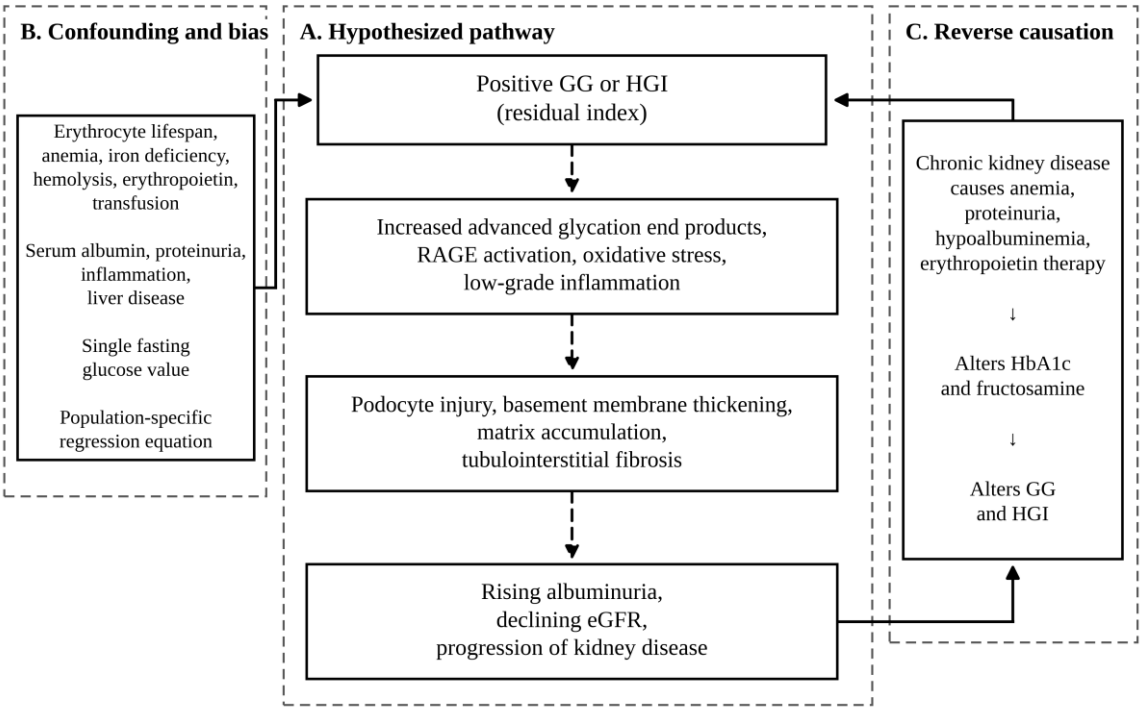
Both GG and HGI contain HbA1c within their formulae, so their association with complications may in part simply reflect HbA1c itself. Because HGI equals measured HbA1c minus predicted HbA1c, it is always mathematically correlated with HbA1c, and this correlation strengthens as the fit of the glucose-HbA1c equation weakens. If renal outcomes are also associated with HbA1c, part of the association between HGI and outcome may derive from that mathematical dependence. Entering HbA1c and HGI simultaneously into a regression model readily produces collinearity and coefficients that are difficult to interpret; if the model fails to handle the part-whole relationship, collinearity and measurement error, effect estimates may be inflated. Dividing GG or HGI into tertiles discards continuous information and creates cut-off points that hold only for one population. Deriving a prediction equation and then testing its prognostic value in the same sample can cause overfitting, whereas applying an equation from another population risks systematic bias. For HGI, using a single fasting glucose value as the predictor adds further measurement error and does not adequately represent long-term glucose exposure [9].

3.3. PATHOPHYSIOLOGICAL BASIS LINKING THE GLYCATION PHENOTYPE TO KIDNEY INJURY

Diabetic kidney disease results from the interaction of glomerular hemodynamic disturbance, activation of the renin-angiotensin system, increased sodium-glucose reabsorption in the proximal tubule, oxidative stress, inflammation, metabolic derangement and fibrosis. Raised intraglomerular pressure together with podocyte and basement membrane injury gives rise to albuminuria; over time, accumulation of extracellular matrix, mesangial expansion and tubulointerstitial fibrosis led to a fall in eGFR.

One hypothesis holds that a high GG or HGI represents a level of tissue glycation greater than that implied by measured glucose, and is therefore accompanied by increased AGEs, endothelial injury and an inflammatory response. A second hypothesis regards these indices merely as markers of a longer erythrocyte lifespan or of differences in glucose transport, without themselves causing renal injury. In the opposite direction, renal failure, anemia, proteinuria and erythropoietin therapy all alter HbA1c or fructosamine and thereby alter GG and HGI themselves, creating reverse causation. In addition, changes in erythrocytes and circulating proteins usually act as confounders or sources of measurement bias rather than lying on the causal path to renal injury. Cross-sectional studies cannot determine whether GG and HGI are a cause, a consequence or merely a concomitant marker of renal injury; these three possibilities are shown separately in Figure 2 [8,9].

Clinically, albuminuria and eGFR reflect two axes of injury that do not run entirely in parallel. Some patients show a falling eGFR without overt albuminuria, whereas others have persistent albuminuria with preserved eGFR. The value of GG and HGI therefore needs to be assessed against several outcomes: incident UACR ≥ 30 mg/g, progression from A1 to A2 or A3, the annual eGFR slope, an eGFR decline of ≥ 30% or ≥ 40%, end-stage kidney disease and composite renal outcomes.



Dashed arrows: hypothesized relationships, not proven to be causal.
Solid arrows: effects on measurement, or documented reverse causation.
Factors in blocks B and C do not lie on the causal path from GG or HGI to kidney injury; they may act as confounders, sources of measurement bias or consequences of kidney disease.

Figure 2. Hypothesized model of the relationship between the glycation gap, the hemoglobin glycation index and diabetic kidney injury [2,5,8,9,20]. Block A is the hypothesized pathway, block B comprises confounders and sources of measurement bias, and block C represents reverse causation. AGEs: advanced glycation end products; RAGE: receptor for AGEs; eGFR: estimated glomerular filtration rate.

3.4. CLINICAL EVIDENCE ON THE GLYCATION GAP

The seminal study by Cohen et al. was conducted in 153 patients with diabetes, including both type 1 and type 2, in whom GG ranged from -3.2% to 5.5% and was relatively stable across two measurements taken 23 ± 2 weeks apart (r = 0.81). The analysis relating to kidney disease was performed only in a subgroup of 40 patients with type 1 diabetes of at least 15 years' duration: GG was -0.8 ± 0.2% in those without kidney disease, -0.3 ± 0.2% in those with moderately increased albuminuria or hypertension, and 0.7 ± 0.3% in those with proteinuria or impaired renal function; each 1% increase in GG was accompanied by a 2.9-fold greater frequency of advancing nephropathy stage (p = 0.0014) [5]. Direct evidence in type 2 diabetes comes from three larger studies. Rodríguez-Segade et al. followed 2,314 patients with type 2 diabetes for a mean of 6.5 years, calculating GG from a repeated-measures regression of HbA1c on fructosamine, and showed that GG predicted progression of kidney disease independently of fructosamine and remained significant after adjustment for HbA1c; the Cox analysis in that study could not establish whether HbA1c or GG was the stronger predictor [10]. Cosson et al. examined 925 patients with type 2 diabetes in a cross-sectional study and found GG to be associated with macroproteinuria and 24-hour proteinuria independently of HbA1c, serum albumin and several other confounders, whereas GG was not consistently associated with retinopathy or peripheral neuropathy [11]. Nayak et al. analyzed 3,182 patients with diabetes and found that UACR rose progressively from the negative through the intermediate to the positive GG group, while GG was also associated with mortality and vascular complications; the population of that study was not separated by type of diabetes, which limits its directness with respect to the scope of this review [12].

In Vietnam, a cross-sectional study of 50 patients with diabetic kidney disease reported a mean GG close to zero, ranging from -1.8% to 1.4%, with significant differences in proteinuria and eGFR between GG groups [13]. In 2024, another Vietnamese study again showed that GG correlated with UACR and eGFR in patients with type 2 diabetes [14]. In the opposite direction, Nguyen Chi Tuong et al. studied 222 patients with newly diagnosed type 2 diabetes in Bac Lieu and found no independent association between GG and moderately increased albuminuria (A2, UACR 30-300 mg/g); the independently associated factors in that sample were hypertension, HbA1c ≥ 7% and eGFR < 60 mL/min/1.73 m² [15]. Differences between studies may stem from disease stage, the prevalence of albuminuria, the way the GG equation was constructed, sample size, serum albumin characteristics and the cross-sectional design itself.

Stratifying by design clarifies the picture. Cross-sectional studies show that a positive GG is associated with severe albuminuria or prevalent kidney disease, but they do not permit conclusions about predictive ability. Only one large longitudinal cohort in type 2 diabetes has demonstrated that GG predicts progression of kidney disease after adjustment for HbA1c [10]. The association with very early renal injury is less consistent, as illustrated by the negative finding in newly diagnosed patients [15]. Most studies are single center, use different GG equations and have not been compared against CGM, so the consistency and generalizability of the evidence remain limited. GG is also subject to a double measurement error, from both HbA1c and fructosamine: in patients with heavy proteinuria, hypoalbuminemia lowers fructosamine and may produce a falsely positive GG.

3.5. CLINICAL EVIDENCE ON THE HEMOGLOBIN GLYCATION INDEX

Lin et al. followed 780 patients with type 2 diabetes at low baseline risk of chronic kidney disease for a median of 7.3 years; a high HGI predicted rapid decline in renal function but did not predict the onset of macroalbuminuria [16]. In a cross-sectional study of 1,622 inpatients in China, the prevalence of diabetic kidney disease rose from 16.6% to 24.2% and then 31.3% across the three HGI tertiles, and the association persisted after multivariable adjustment [17]. Because of the cross-sectional design, the latter finding reflects only an association with prevalent kidney disease rather than predictive ability.

Two recently published cohorts provide more direct longitudinal evidence in type 2 diabetes. Zhou et al. retrospectively followed 1,050 newly diagnosed patients with normal baseline renal function for a mean of 10.95 years; 307 developed diabetic kidney disease. The relationship between HGI and the risk of kidney disease was U-shaped: the highest HGI quartile carried an increased risk (OR 1.54; 95% CI 1.03-2.30) and the lowest quartile also showed a trend towards higher risk that did not reach statistical significance (OR 1.40; 95% CI 0.92-2.14), whereas HGI treated as a continuous variable was no longer associated with the outcome after full adjustment [18]. The 5-year cohort of Kuo et al. followed 441 adults with type 2 diabetes, with renal progression defined as new-onset albuminuria or an eGFR decline of at least 30%; after a median of 61 months, 162 patients (36.7%) had an event, and the highest tertile of first-year mean HGI carried a 58% higher risk than the lowest tertile in the fully adjusted model (HR 1.58; 95% CI 1.01-2.49) [19]. The confidence interval for this estimate lies close to unity, and the U-shaped relationship reported by Zhou et al. indicates that grouping by tertile or quartile may substantially influence the conclusion.

In the same study by Kuo et al., HbA1c was associated with renal progression, whereas HGI did not independently predict incident retinopathy or mortality after full adjustment. Cardoso et al. analyzed an original prospective cohort of 687 patients with type 2 diabetes followed for a median of 10.6 years, comparing baseline HGI, first-year mean HGI and HGI variability directly against HbA1c; this was an analysis of the authors' own cohort data rather than a systematic review or meta-analysis. HGI predicted outcomes as well as HbA1c but no better, and the authors concluded that HGI cannot yet be recommended for clinical use [20]. Taking together, the longitudinal evidence supports the view that HGI carries information about renal risk, but its incremental predictive value beyond HbA1c, UACR and eGFR has not been established, because most studies have not reported the change in C-statistic, model calibration or the capacity for risk reclassification.

Table 2. Selected studies on GG/HGI and renal outcomes

Study	Design, population, follow-up	Index and calculation	Renal outcome	Main findings and risk of bias
Cohen et al., 2003 [5]	Cross-sectional with repeated measurements; 153 patients with type 1 and type 2 diabetes; the nephropathy analysis was confined to 40 patients with type 1 diabetes of ≥ 15 years' duration	GG; HbA1c predicted from fructosamine using regression within the study sample	Nephropathy stage across three groups	GG was -0.8 ± 0.2%, -0.3 ± 0.2% and 0.7 ± 0.3% across the three nephropathy levels. Each 1% increase in GG was accompanied by a 2.9-fold greater frequency of advancing nephropathy stage (p = 0.0014); the source publication does not state whether this is an odds ratio or a risk ratio. Small sample, type 1 population, not direct evidence for type 2 diabetes. Risk of bias: high
Rodríguez-Segade et al., 2011 [10]	Longitudinal cohort; 2,314 patients with type 2 diabetes; mean follow-up 6.5 years	GG; HbA1c regressed on fructosamine using a repeated-measures model, calculated at each visit	Progression of nephropathy by albumin excretion category	GG predicted progression of kidney disease independently of fructosamine and remained significant after adjustment for HbA1c (Cox model). The analysis could not determine whether HbA1c or GG was the stronger predictor. Risk of bias: moderate
Cosson et al., 2013 [11]	Cross-sectional; 925 patients with type 2 diabetes	GG from fructosamine; regression equation from the study population	Macroproteinuria; 24-hour proteinuria	GG was associated with macroproteinuria independently of HbA1c and serum albumin; no consistent association with retinopathy or peripheral neuropathy. Cross-sectional design permits conclusions about association only. Risk of bias: moderate
Nayak et al., 2013 [12]	Cohort; 3,182 patients with diabetes, not separated into type 1 and type 2	GG; standardized HbA1c predicted from fructosamine	UACR; mortality and vascular complications	UACR rose progressively from the negative through the intermediate to the positive GG group; GG was associated with mortality and vascular complications. The mixed diabetes population reduces directness with respect to the scope of this review. Risk of bias: moderate
Le Quoc Tuan et al., 2022 [13]	Cross-sectional; 50 patients with diabetic kidney disease in Vietnam	GG from fructosamine; equation derived within the study sample	Proteinuria; eGFR	Mean GG close to zero, ranging from -1.8% to 1.4%; proteinuria and eGFR differed between GG groups. Small sample; no effect estimates reported. Risk of bias: high
Le TQ et al., 2024 [14]	Cross-sectional; patients with type 2 diabetes in Vietnam	GG from fructosamine	UACR; eGFR	GG correlated with UACR and eGFR. Cross-sectional design; confirmation in longitudinal studies is required. Risk of bias: moderate
Nguyen Chi Tuong et al., 2024 [15]	Cross-sectional; 222 patients with newly diagnosed type 2 diabetes, Bac Lieu	GG from fructosamine	Moderately increased albuminuria (A2, UACR 30-300 mg/g)	No independent association between GG and A2 albuminuria; the independently associated factors were hypertension, HbA1c ≥ 7% and

Study	Design, population, follow-up	Index and calculation	Renal outcome	Main findings and risk of bias
				eGFR < 60 mL/min/1.73 m². Risk of bias: moderate
Lin et al., 2022 [16]	Retrospective cohort; 780 patients with type 2 diabetes at low baseline risk of chronic kidney disease; median follow-up 7.3 years	HGI from fasting plasma glucose; equation from the study population	Rapid eGFR decline; onset of macroalbuminuria	A high HGI predicted rapid decline in renal function but did not predict the onset of macroalbuminuria. Single-center, retrospective, based on a single fasting glucose value. Risk of bias: moderate
Xin et al., 2023 [17]	Cross-sectional, inpatients; 1,622 patients with type 2 diabetes in China	HGI from fasting plasma glucose; grouped by tertile	Prevalent diabetic kidney disease	The prevalence of kidney disease rose from 16.6% to 24.2% and then 31.3% across the three HGI tertiles; the association persisted after multivariable adjustment. Being cross-sectional, this reflects association with prevalent disease only. Risk of bias: moderate
Zhou et al., 2025 [18]	Single-center retrospective cohort; 1,050 patients with newly diagnosed type 2 diabetes and normal baseline renal function; mean follow-up 10.95 years	HGI from fasting plasma glucose; regression equation derived from the study sample; grouped by quartile	Incident diabetic kidney disease (UACR ≥ 30 mg/g persisting ≥ 3 months and/or eGFR < 60 mL/min/1.73 m²)	307 of 1,050 patients had an event. U-shaped relationship: highest quartile OR 1.54 (95% CI 1.03-2.30); lowest quartile OR 1.40 (95% CI 0.92-2.14), not statistically significant. HGI as a continuous variable was no longer associated after full adjustment. Retrospective, single center. Risk of bias: moderate
Kuo et al., 2026 [19]	Prospective cohort; 441 patients with type 2 diabetes; median follow-up 61 months	HGI from fasting plasma glucose; baseline HGI and first-year mean HGI, grouped by tertile	New-onset albuminuria or eGFR decline ≥ 30%	162 of 441 patients (36.7%) had an event. Highest tertile of first-year mean HGI: HR 1.58 (95% CI 1.01-2.49) versus the lowest tertile after full adjustment; the confidence interval lies close to unity. Risk of bias: low to moderate
Cardoso et al., 2024 [20]	Prospective cohort; 687 patients with type 2 diabetes; median follow-up 10.6 years	Baseline HGI, first-year mean HGI and HGI variability, compared directly against HbA1c	Incident albuminuria, macroalbuminuria, progressive renal failure	HGI predicted outcomes as well as HbA1c but no better; the authors concluded that HGI cannot yet be recommended for clinical use. This is an original cohort analysis, not a systematic review. Risk of bias: low

Note: eGFR: estimated glomerular filtration rate; GG: glycation gap; HGI: hemoglobin glycation index; HR: hazard ratio; CI: confidence interval; OR: odds ratio; UACR: urinary albumin-to-creatinine ratio.

3.6. CONFOUNDING FACTORS IN CHRONIC KIDNEY DISEASE

3.6.1. Anemia and altered erythrocyte lifespan

Anemia is common as eGFR falls, owing to reduced erythropoietin, iron deficiency, inflammation, blood loss and a shortened erythrocyte lifespan. Hemolysis, hemorrhage or erythropoietin therapy increases the proportion of young red cells and usually lowers HbA1c relative to glucose, whereas untreated iron deficiency

may spuriously raise it. Transfusion has an unpredictable effect that depends on the donor's HbA1c and the degree of dilution. These changes are sufficient to render HGI negative or positive without reflecting any intrinsic glycation phenotype [2,3].

3.6.2. Serum albumin, proteinuria and protein turnover

Fructosamine and glycated albumin depend on both the extent of glycation and the amount and age of circulating protein. Heavy proteinuria, nephrotic syndrome, malnutrition, inflammation, liver disease and peritoneal dialysis all alter serum albumin and its half-life and may therefore produce a falsely positive GG. Correcting fructosamine for albumin, or using glycated albumin instead, reduces part of this bias but does not remove the effect of protein turnover [2,4].

3.6.3. Fasting glucose does not fully represent glucose exposure

An HGI based on a single fasting glucose sample is easily biased when postprandial glucose predominates, when the dawn phenomenon is present, when basal insulin is used, or when glucose variability is high. A single day's glucose is also a poor representation of an HbA1c that reflects 2-3 months. An HGI calculated from multiple measurements or from CGM has a stronger physiological basis but requires data over an adequate period and a sensor of sufficient quality.

3.6.4. Stage of kidney disease, dialysis and concurrent treatment

In chronic kidney disease stages G4-G5, the accuracy of HbA1c falls markedly, particularly in patients on dialysis. Uremia, metabolic acidosis, inflammation, “burnt-out diabetes”, altered insulin clearance and the dialysis cycle together make glucose fluctuate in complex ways. SGLT2 inhibitors increase urinary glucose excretion and may alter the relationship between fasting glucose, mean glucose and HbA1c, while insulin and sulfonylureas increase the risk of hypoglycemia. An HGI equation derived in patients with mild chronic kidney disease should therefore not be applied directly to patients on dialysis.

3.7. THE ROLE OF CGM AND GMI WHEN HbA1c IS DISCORDANT

CGM measures interstitial glucose many times a day, allowing assessment of mean glucose, time in target range, time in hypoglycemia and the degree of glucose variability. Studies in chronic kidney disease show that HbA1c, fructosamine and glycated albumin all deviate from CGM-derived glucose at the individual level, and that no indirect marker is optimal across all disease stages [21]. Substantial differences between HbA1c and GMI are also common in this group, reflecting the combined influence of anemia, eGFR, treatment and sensor data quality. A 2025 consensus report emphasized the role of CGM in detecting hypoglycemia, assessing variability and supporting the management of patients with advanced chronic kidney disease or dialysis, while evidence for improvement in long-term renal outcomes remains limited [21]. GMI is not a “true” HbA1c and should not be substituted mechanically. When HbA1c and GMI diverge, clinicians should review CGM data quality, sensor wear time, anemia, iron stores, transfusion history, erythropoietin therapy, proteinuria, albumin and any changes in the treatment regimen. The HbA1c-GMI difference may itself be regarded as a CGM-based form of HGI, but the definition must be standardized before it can be used prognostically.

3.8. CURRENT CLINICAL VALUE

The approach presented in this section is a proposal by the authors based on the available evidence, not an official ADA or KDIGO algorithm. GG or HGI may be useful as a supplementary marker when HbA1c is discordant with self-monitored glucose, with CGM data or with the clinical picture; when HbA1c changes out of proportion to treatment; and in research requiring stratification by glycation phenotype. These indices help clinicians identify patients whose HbA1c is “higher than expected” or “lower than expected” and thereby avoid intensifying treatment because of the HbA1c value alone when direct glucose data do not support it.

GG and HGI should not currently be used in isolation to diagnose diabetic kidney disease, to replace UACR and eGFR, to decide on kidney-protective therapy or to set HbA1c targets. No threshold has been recommended by ADA or KDIGO, and the equations and cut-off points differ between studies. Nor should insulin be increased solely because HGI is positive when CGM shows glucose within target, since this readily leads to hypoglycemia.

When discordance is suspected, HbA1c should first be confirmed with a standardized assay and compared against capillary glucose or CGM. The next step is to assess the full blood count, ferritin, evidence of hemolysis or blood loss, transfusion history, erythropoietin therapy, eGFR, albumin and proteinuria. If erythrocyte-related factors predominate, directly measured glucose or CGM should be preferred; if CGM data are unavailable and albumin is stable, fructosamine or glycated albumin may be considered. GG and HGI should serve only as an additional layer of interpretive information and not replace comprehensive clinical assessment. This sequence has not been validated prospectively and should be regarded as a reference framework rather than a recommendation. Both ADA 2026 and KDIGO recommend continuing to use HbA1c for long-term monitoring, with caution in advanced chronic kidney disease; CGM or self-monitoring of glucose is preferred when HbA1c is discordant or when the regimen carries a risk of hypoglycemia [1,2,21]. Neither current guideline has incorporated GG or HGI into a routine algorithm.

3.9. RESEARCH GAPS AND DIRECTIONS FOR VIETNAM

Vietnamese data consist mainly of cross-sectional studies with small to moderate sample sizes, focused on GG calculated from fructosamine. No externally validated reference equation exists for the Vietnamese population, and the influence of age, sex, anemia, eGFR, albumin, proteinuria, glucose-lowering drugs and regional differences remains unclear. Findings on the association with moderately increased albuminuria have so far been inconsistent [13-15]. Future research should prioritize multicenter cohort designs with simultaneous measurement of HbA1c, fructosamine, glycated albumin and CGM, deriving prediction equations in a training set and validating them in an independent set, while assessing UACR, eGFR slope and hard renal events. Analyses need to adjust for anemia, iron stores, erythropoietin, albumin, inflammation, medication and glucose variability. Incremental value should be quantified through the change in C-statistics, calibration, risk reclassification and clinical decision analysis, rather than by reporting correlation coefficients or p values alone. Another important direction is to clarify whether GG and HGI represent a biological mechanism amenable to intervention or are simply markers. Research integrating AGEs, RAGE, oxidative stress, inflammatory markers, genetic data and proteomics could map the path from glycation phenotype to podocyte injury and fibrosis. Any addition of further biomarkers must still rest on improved prediction and altered treatment decisions, avoiding the creation of a complex test that does not change patient care.

4. CONCLUSION

GG and HGI quantify the residual between HbA1c and either fructosamine or glucose and may thereby reflect the combined influence of several biological and measurement-related sources of variation. In type 2 diabetes, cross-sectional studies show that both indices are associated with albuminuria and prevalent kidney disease, while cohort studies report an association with progression of kidney disease, with evidence from 2025 and 2026 suggesting that the relationship may not be linear. Findings remain inconsistent across studies, the method of calculation is not standardized, and both indices are strongly influenced by erythrocytes, albumin, the stage of chronic kidney disease and their mathematical dependence on HbA1c. In current practice, GG and HGI should be regarded as supplementary markers that help interpret an HbA1c value discordant with directly measured glucose, rather than as replacements for HbA1c, CGM, UACR or eGFR; their incremental predictive value beyond these measures has not been established. Before thresholds, prognostic value and a clinical algorithm can be defined, Vietnam needs longitudinal, multicenter studies that incorporate CGM.

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Declaration of Competing Interest

The authors declare no financial conflict of interest and no personal relationship that could have influenced the work reported in this article.

Declaration of Generative AI and AI-Assisted Technologies

The authors did not use artificial intelligence software in the writing of this article.

Author contributions

All authors read and revised the manuscript and approved its final version; Tran Dang Dang Khoa is responsible for correspondence.

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KHOẢNG TRỐNG GLYCAT HÓA VÀ CHỈ SỐ GLYCAT HÓA HEMOGLOBIN TRONG BỆNH THẬN DO ĐÁI THÁO ĐƯỜNG TÍP 2: CƠ SỞ SINH LÝ BỆNH, BẰNG CHỨNG LÂM SÀNG VÀ TRIỂN VỌNG ỨNG DỤNG

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Mục tiêu: Tổng hợp cơ sở sinh lý bệnh, cách xác định và bằng chứng lâm sàng về khoảng trống glycat hóa (glycation gap - GG) và chỉ số glycat hóa hemoglobin (hemoglobin glycation index - HGI) trong bệnh thận do đái tháo đường típ 2. **Phương pháp:** Tổng quan tường thuật có cấu trúc; tìm tài liệu trên PubMed/MEDLINE, Cochrane Library, Google Scholar cùng trang chính thức của Hiệp hội Đái tháo đường Hoa Kỳ và KDIGO đến ngày 31/7/2026, kèm tiêu chí lựa chọn, tiêu chí loại trừ và xếp loại nguy cơ sai lệch cho từng nghiên cứu. **Kết quả:** GG và HGI là các chỉ số phần dư giữa HbA1c đo được với HbA1c dự đoán từ fructosamine hoặc từ glucose. Cả hai phản ánh tổng hợp nhiều nguồn biến thiên sinh học và đo lường chứ không riêng khả năng glycat hóa hemoglobin, đồng thời phụ thuộc phương trình hồi quy của từng quần thể nên không so sánh trực tiếp được giữa các nghiên cứu. Nghiên cứu cắt ngang cho thấy GG hoặc HGI cao liên quan với albumin niệu và bệnh thận hiện mắc. Trên đái tháo đường típ 2, đoàn hệ 5 năm ghi nhận nhóm HGI trung bình năm đầu cao nhất có nguy cơ tiến triển thận tăng 58% (HR 1,58; KTC 95%: 1,01-2,49), trong khi một đoàn hệ 1.050 người bệnh cho thấy quan hệ hình chữ U giữa HGI và bệnh thận mới mắc. Giá trị dự báo tăng thêm ngoài HbA1c, tỷ số albumin/creatinin niệu và mức lọc cầu thận chưa được xác lập đầy đủ. Thiếu máu, thay đổi đời sống hồng cầu, điều trị erythropoietin, giảm albumin máu và protein niệu đều có thể làm sai lệch hai chỉ số. **Kết luận:** GG và HGI có thể hỗ trợ giải thích một giá trị HbA1c không phù hợp với glucose đo trực tiếp. Bằng chứng hiện có chưa đủ để sử dụng hai chỉ số này một cách độc lập trong chẩn đoán, phân tầng nguy cơ hay điều chỉnh điều trị bệnh thận do đái tháo đường.

Từ khóa: khoảng trống glycat hóa; chỉ số glycat hóa hemoglobin; bệnh thận do đái tháo đường; HbA1c; albumin niệu.