Malays J Pathol 2026; 48(1): 125 – 131

ORIGINAL ARTICLE

Haemoglobin glycation index as an independent predictor of diabetic kidney disease in type 2 diabetes mellitus: a retrospective analysis

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Abstract

Introduction: The haemoglobin glycation index (HGI) reflects individual variations in glycation tendency and may offer additional value beyond HbA1c in predicting diabetes-related complications. This study aimed to evaluate the association and predictive value of HGI for diabetic kidney disease (DKD) in patients with type 2 diabetes mellitus (T2DM). *Materials and Methods:* A total of 400 T2DM patients were enrolled. Predicted HbA1c was calculated using a linear regression equation (R^2=0.454) derived from fasting plasma glucose (FPG) and HGI was defined as the difference between measured and predicted HbA1c. Paired t-tests and Pearson correlation assessed the relationship between measured and predicted HbA1c. Multivariate logistic regression and receiver operating characteristic (ROC) analysis used to evaluate HGI as a predictor of DKD. *Results:* A strong positive correlation observed (r=0.674, p<0.001) between measured and predicted HbA1c and no significant difference observed (p=0.964) among the T2DM population. DKD was identified in 192 participants, who demonstrated significantly higher HGI compared to non-DKD patients (p=0.002). Multivariate analysis showed HGI (OR: 1.249, 95% CI: 1.053–1.482, p=0.011) and eGFR (OR: 0.964, 95% CI: 0.952–0.976, p<0.001) were independent risk factors for DKD. ROC analysis showed HGI as a moderate predictor of DKD (AUC=0.722, p<0.001), with an optimal cutoff of 0.53 carries 56.3% sensitivity and 81.2% specificity. *Conclusion:* HGI is independently associated with DKD in T2DM and may serve as a useful adjunct marker, complimenting HbA1c and urinary albumin-to-creatinine ratio (UACR) for early identification of those at increased risk of kidney complications.

Keywords: Haemoglobin glycation index, Diabetic kidney disease, HbA1c, Predicted HbA1c

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a major public health concern globally including Malaysia. It is the most common form of diabetes which accounts for >90% of all cases of adult-onset diabetes mellitus.[1] In 2019, the prevalence of diabetes in Malaysia in adults ≥ 18 years was 18.3% which was increasing from 13.4% in 2015.[2] A meta-analysis of 15 studies from 1995 to 2021 showed that the pooled prevalence of T2DM was 14.39%.[3] The forefront of managing T2DM involves maintaining optimal glycaemic control. Persistent symptoms of high blood glucose or low blood glucose may lead to diabetic complications, such as neuropathy, nephropathy, retinopathy, and cardiovascular diseases.

Diabetic kidney disease (DKD) which is a microvascular complication, is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease globally.[1] Glycaemic variability (GV) or blood glucose fluctuations, refers to dynamic changes in glucose levels ranging from low to high, encompasses both short-term variations, such as within-day and between-day changes, and long-term fluctuations occurring over weeks, months, or years.[4] GV which reflects excessive glucose excursions and serves as an indicator of glucose homeostasis, has been associated with increased cardiovascular risk due to postprandial spikes and hypoglycaemic events in individuals with type 2 diabetes.[5,6]

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Despite increasing recognition of GV as a contributor to diabetes-related complications, its specific impact on DKD remains poorly understood. Understanding the influence of GV on DKD development is therefore crucial for improving risk stratification and management strategies in this population. However, current methods for assessing GV, such as self-monitored blood glucose, are uncomfortable for patients and costly to maintain in outpatient settings. Although continuous glucose monitoring systems (CGMS) provide a more comprehensive assessment of glucose fluctuations, they remain limited by high cost, complex data interpretation, and lack of standardised thresholds for GV indices.[4,5]

According to local guidelines, HbA1c remains the standard marker for assessing glycaemic control over the preceding three months and is strongly predictive of diabetes-related complications. Higher HbA1c levels are commonly observed in patients with DKD, while maintaining HbA1c below 7% reduces complication risk.[7,8] Nevertheless, HbA1c does not capture short-term glycaemic fluctuations, limiting its utility in evaluating individual's GV and may not accurately reflect true glycaemia in conditions affecting red blood cell lifespan, such as anaemia, liver disease, or chronic kidney disease.[9] The haemoglobin glycation index (HGI) offers a complementary measure of glycaemic control because reflects both long-term and short-term glucose patterns and has been associated with cardiovascular and microvascular complications.[6,10,11] Despite these findings, the relationship between HGI and DKD in patients with T2DM remains insufficiently explored.

This study aimed to determine the relationship between fasting plasma glucose- (FPG-) derived predicted HbA1c and measured HbA1c and the value of HGI in predicting DKD among T2DM patients.

MATERIALS AND METHODS

Study design and sample size calculation

This retrospective single-centre study at a tertiary teaching hospital included 400 patients with T2DM who were followed up between April 2023 and December 2024. The sample size was calculated using the Fisher's Z transformation formula for correlation studies, with a power of 80% and a type 1 error of 5% (Z1-alpha/2 = 1.96, Z1-beta = 0.84). Based on the correlation coefficient of p=0.14 reported by Xin *et al*,[10] the minimum required sample size was 398. T2DM was defined according to the Malaysia Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus 6th edition (2020).[2] The exclusion criteria were: (1) Incomplete laboratory data for HbA1c, FBG and Serum creatinine levels, (2) Incomplete demographic data for Age, Sex and Race, (3) Same patients with follow-up visits within the study duration, (4) Type 1 diabetes, (5) gestational diabetes, (6) Patients admitted to the ward for acute complications of diabetes like diabetes ketoacidosis (DKA) or hyperosmolar hyperglycaemic state (HHS) in the period of data collection, (7) Recent acute kidney injury, (8) Patients admitted twice or more times for diabetes-related diseases like DKA and HHS and (9) Primary renal parenchyma disease.

Ethical approval

This research is approved by the Research Ethics Committee, The National University of Malaysia (RECUKM) with the reference number JEP-2024-521.

Data collection and analysis

Demographic data, including age, gender, duration of diabetes, blood pressure, and body mass index (BMI), were retrieved from patient records in the Caring Hospital Enterprise System (c-HetS). Laboratory data, including FPG, HbA1c, creatinine, and urinary albumin-to-creatinine ratio (UACR), were obtained from the Integrated Laboratory Management System (ILMS). HbA1c was analysed using ion-exchange high-performance liquid chromatography (HPLC) and capillary electrophoresis, while FPG was measured using an enzymatic method on the Architect and Alinity c systems. Method comparability for both assays was verified in accordance with CLSI protocols. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the CKD-EPI 2021 equation.[12] Diagnosis of DKD was then made clinically based on albuminuria and/or reduced eGFR persisted >3 months in the presence of diabetes and without any other kidney diseases causes.[2]

Calculation of HGI

A linear regression model was constructed using baseline FPG and HbA1c data. A linear regression equation was established to calculate predicted HbA1c, Predicted HbA1c = 4.637 + 0.429*FPG ($r=0.674$, $p<0.001$) (FIG 1). Measured HbA1c then subtracted predicted HbA1c to generate HGI (HGI = measured HbA1c – predicted HbA1c).

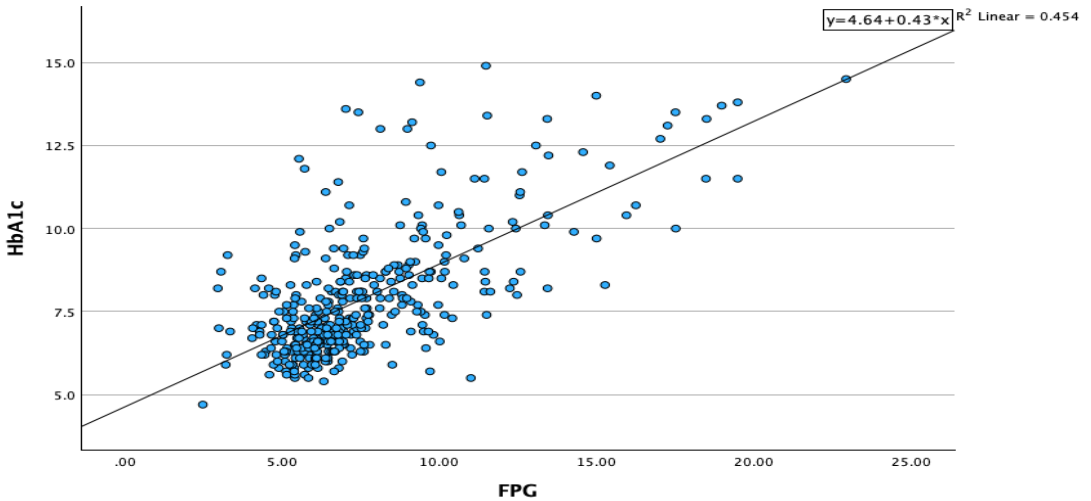

FIG. 1 Correlation between HbA1c and FPG. The predicted HbA1c was defined as follows: Predicted HbA1c = 4.637 + 0.429 *FPG (r=0.674, p<0.001)

Statistical Analysis

All data were analysed using the SPSS version 29.0, IBM Corp, USA. Normally distributed data was expressed as mean (SD) and non-normally distributed data was expressed as median (IQR). Categorical variables were reported as medians and percentages. Paired t-test was used to compare the difference while Pearson correlation coefficient was used to determine the correlation between the predicted and measured HbA1c. Independant t-test was used for the association between HGI and DKD. Logistic regression method was used for analysis of risk factors of DKD with T2DM. Receiver operating characteristic (ROC) analysis was conducted to evaluate HGI as a predictor of DKD. A p-value of <0.05 is considered statistically significant.

RESULTS

TABLE 1 summarises the demographic and biochemical characteristics of the study participants. The overall mean age was 59.01 years, with 39.5% (158 out of 400) being male, and the majority were of Malay ethnicity (68.3%, 273 out of 400). The DKD group exhibited a higher mean age (61 years versus 56 years), longer duration of diabetes (13 years versus 8 years), and higher HbA1c levels (8.3% versus 7.4%) compared to the non-DKD group, indicating poorer glycaemic control among those with kidney involvement. Moreover, the DKD group showed significantly higher UACR and HGI values, while the mean predicted HbA1c and FPG levels were only slightly elevated. No substantial differences were observed in systolic blood pressure, diastolic blood pressure, or BMI between the two groups.

Comparison between measured and predicted HbA1c values across all 400 data points revealed no significant difference (p=0.964). Pearson correlation analysis demonstrated a strong positive correlation between measured and predicted HbA1c (r=0.674, p<0.001) (FIG 1). These findings confirm the reliability of the regression model in estimating HbA1c from FPG and validate its use in deriving the HGI for this study.

Independant t-test analysis confirmed that the mean HGI was significantly higher in the DKD group compared to the non-DKD group (p = 0.002). Although this difference was statistically significant, the effect size was small to moderate (Cohen's d = 0.317), suggesting that additional factors may contribute to DKD development. On univariate analysis, age, gender, duration of diabetes, systolic blood pressure (SBP), FPG, eGFR, UACR, and HGI were all significantly associated with DKD (p < 0.05) (TABLE 2).

Multivariate logistic regression analysis further identified eGFR (OR: 0.964, 95% CI: 0.952–0.976, p < 0.001) and HGI (OR: 1.249,

TABLE 1: Demographic and biochemical characteristics of study participants

Variables		Total (n=400)	With DKD (n=192)	Without DKD (n=208)
Age (years)[&]		59.01 (13.231)	61.29 (13.086)	56.90 (13.046)
Gender[#]	Male	158 (39.5%)	86 (44.8%)	72 (34.6%)
	Female	242 (60.5%)	106 (55.2%)	136 (65.4%)
Race[#]	Malay	273 (68.3%)	138 (71.9%)	135(64.9%)
	Chinese	84 (21%)	34 (17.7%)	50 (24.0%)
	Indian	38 (9.5%)	17 (8.9%)	21(10.1%)
	Others	5 (1.3%)	3 (1.5%)	2 (1.0%)
Duration of T2DM (years)^		10 (14)	13 (13.75)	8.0 (12.75)
Systolic Blood Pressure (mmHg)[&]		136.78 (16.495)	138.84 (16.699)	134.87 (16.11)
Diastolic Blood Pressure (mmHg)[&]		76.17 (10.565)	75.69 (11.374)	76.61(9.765)
BMI (kg/m^2)[&]		28.9532 (5.56545)	29.2736 (5.41802)	28.6574 (5.69517)
HbA1c (%)[&]		7.897 (1.8927)	8.387 (2.1779)	7.444 (1.4491)
pHbA1c (%)[&]		7.8936 (1.27353)	8.1559 (1.53685)	7.6515 (0.90785)
FPG (mmol/L)[&]		7.5912 (2.96861)	8.2026 (3.58239)	7.0268 (2.11620)
eGFR (mL/min/1.73m2m)[&]		86.83 (24.059)	77.96 (27.134)	95.02 (17.202)
UACR (mg/mmol)^		3.350 (10.8)	10.7 (30.8)	1.7 (2.0)
HGI (%)[&]		0.0031 (1.39909)	0.2311 (1.55382)	-0.2073 (1.20524)

TDKD (Diabetic Kidney Disease); T2DM (Type 2 diabetes Mellitus); BMI (Body Mass Index); pHbA1c (Predicted HbA1c); FPG (Fasting Plasma Glucose); eGFR (Estimated Glomerular Filtration Rate); UACR (Urine Albumin-to-Creatinine Ratio); HGI (Haemoglobin Glycation Index); [&]Mean (SD); [#]Frequency (%); ^Median (IQR)

95% CI: 1.053–1.482, p = 0.011) as independent predictors of DKD (TABLE 3). The ROC analysis demonstrated that HGI was a moderate predictor of DKD (AUC = 0.722, 95% CI: 0.671–0.772, p < 0.001), after adjusting for age, duration of T2DM, BMI, and eGFR. The optimal HGI cutoff value for predicting DKD was 0.532, yielding a sensitivity of 56.3% and specificity of 81.2% (FIG 2).

TABLE 2: Univariate Logistic Regression analysis of risk factors for Diabetic Kidney Disease (DKD) in Type 2 Diabetes Mellitus (T2DM)

Variables	β-coefficient	OR (95% CI)	p-value
Age (years)	0.026	1.026 (1.010-1.042)	0.001
Gender	-0.427	0.653 (0.436-0.977)	0.038
Duration of Diabetes (years)	0.047	1.048 (1.023-1.073)	<0.001
Systolic Blood Pressure (mmHg)	0.015	1.015 (1.003-1.027)	0.017
FPG (mmol/L)	0.145	1.157 (1.073-1.247)	<0.001
HGI	0.234	1.264 (1.088-1.469)	0.002
eGFR (ml/min/1.73m^2)	-0.033	0.967 (0.958-0.977)	<0.001
UACR (mg/mmol)	0.157	1.17 (1.116-1.227)	<0.001

OR (odd's ratio); CI (confidence interval); FPG (Fasting Plasma Glucose; HGI (Haemoglobin Glycation Index)); eGFR (Estimated Glomerular Filtration Rate); UACR (Urine Albumin-to-Creatinine Ratio)

TABLE 3: Multivariate Binary Logistic Regression analysis of risk factors for Diabetic Kidney Disease (DKD) in Type 2 Diabetes Mellitus (T2DM)

Variables	β-coefficient	OR (95% CI)	p-value
Age (years)	-0.009	0.991 (0.970-1.013)	0.439
Duration of Diabetes (years)	0.027	1.027 (1.000-1.056)	0.051
BMI (kg/m^2)	0.036	1.037 (0.995-1.080)	0.083
eGFR (ml/min/1.73m^2)	-0.037	0.964 (0.952-0.976)	<0.001*
HGI	0.223	1.249 (1.053-1.482)	0.011*

OR (odd's ratio); CI (confidence interval); BMI (Body Mass Index); eGFR (Estimated Glomerular Filtration Rate); HGI (Haemoglobin Glycation Index); *p<0.05 is significant

DISCUSSION

Earlier investigations have laid the foundation for understanding the clinical relevance of the HGI, beginning with Carette and Czernichow *et al*.[13] who discussed both its potential benefits and limitations. They recognised HGI's value in identifying individuals with atypical glycation patterns and elevated cardiovascular risk while emphasising the need for methodological standardisation before its widespread clinical application.[13,14] Subsequently, Joung *et al*.[14] validated the physiological significance of HGI by demonstrating a strong concordance between the glycation gap and HGI derived from continuous glucose monitoring data, supporting its reliability as a marker of interindividual glycation variability.[13,14]

Further studies expanded the understanding of HGI's prognostic value in renal disease. Lin *et al*.[15] reported that HGI independently predicted renal function decline in patients with T2DM who initially had a low risk of CKD, underscoring its utility in early detection of renal impairment.[15] Similarly, Nakasone *et al*.[16] showed that higher HGI values independently predicted the development of CKD in an apparently healthy population, establishing HGI as a novel risk factor for early renal dysfunction. Tatli[17] also demonstrated that HGI, along with the triglyceride-glucose index, was strongly correlated with albuminuria and reduced eGFR, suggesting their combined potential as metabolic indicators of renal dysfunction, particularly in anaemic individuals where HbA1c interpretation may be affected.

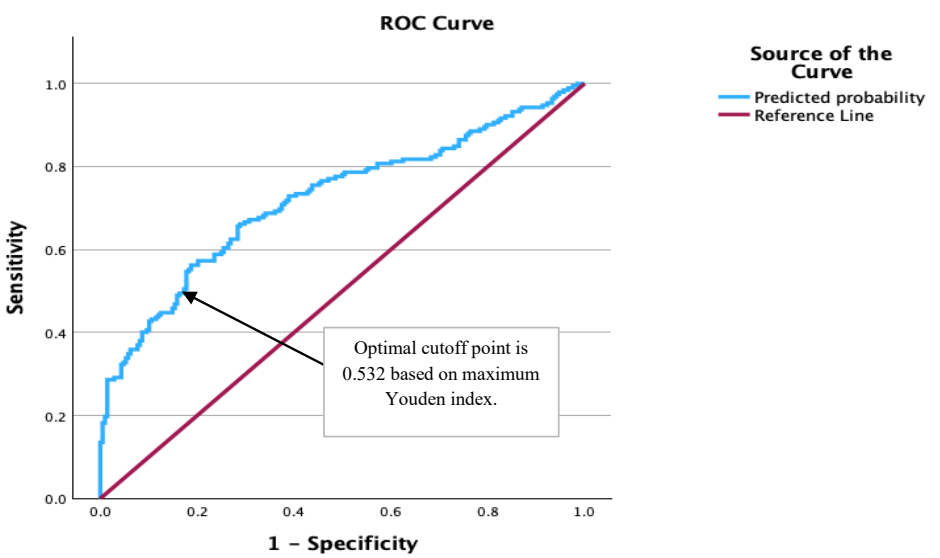

FIG. 2 Receiver operating characteristics curves of diabetic kidney disease (DKD). The area below the receiver operating characteristic (ROC) curve of this model was 0.722 (95% CI:0.671-0.772). The sensitivity and specificity corresponding to the maximum Youden index were 0.563 and 0.812, respectively.

In agreement with these findings, Zhou *et al*.[18] reported that elevated HGI levels were significantly associated with diabetic nephropathy in T2DM patients, even after adjusting for traditional glycaemic indices such as fasting glucose and HbA1c, reinforcing HGI's role as an independent predictor of DKD. Similarly, Xin *et al*.[10] found that higher HGI values were independently associated with DKD in a Chinese inpatient cohort, further supporting HGI as a marker of interindividual glycation variability and a predictor of renal risk beyond conventional glycaemic measures.

In contrast to these earlier populations, our study focusing on outpatient T2DM cohort, is the first conducted in Malaysia and uniquely evaluated an optimal HGI cutoff for predicting DKD among T2DM patients. The findings demonstrated that increased HGI serves as an independent marker for DKD risk, consistent with previous international studies. However, no standardised cutoff value for clinical application has yet been established.

The limitations of this study include its single-centre design, which may not fully represent the broader Malaysian T2DM population, and the lack of data on patient medications (e.g., angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers) that could potentially influence DKD progression. Nevertheless, the consistency of our findings with previous studies suggests that the study design and analytical approach are robust and can partially compensate for unmeasured confounding factors. Furthermore, given the clustering of data points at lower FPG range, future research should employ broader range of glycaemic profiles to enhance generalisability.

Taken together with evidence from previous studies, our findings highlight the potential clinical utility of integrating the HGI into diabetes management frameworks. Because HGI accounts for both FPG and individual glycation tendency, it can complement HbA1c in identifying patients with discordant glycaemic profiles. In clinical practice, incorporating HGI into electronic laboratory reporting systems could help clinicians identify T2DM patients at risk of early DKD, particularly those whose HbA1c values may underestimate glycaemic exposure due to anaemia, renal impairment, or altered red blood cell turnover.[2] This approach could facilitate earlier intervention, optimise glycaemic targets, and reduce the risk of renal and vascular complications.

Future studies should aim to validate these findings in larger, multicentre cohorts and explore the longitudinal relationship between HGI and DKD progression. Incorporating continuous glucose monitoring data could help establish dynamic thresholds for HGI interpretation and improve its predictive accuracy across different populations. Additionally, integrating HGI with other biomarkers like inflammatory or lipid indices may enhance DKD risk stratification. From a public health perspective, establishing population-specific HGI reference ranges and cost-effective analytical pathways would strengthen its clinical applicability, especially in resource-limited settings.

CONCLUSION

In conclusion, predicted HbA1c demonstrated strong correlation with measured HbA1c and may serve as an alternative marker when direct measurement is unavailable. Moreover, HGI can act as a valuable prognostic indicator to identify patients at increased risk of DKD, particularly in resource-limited laboratory settings.

Acknowledgements: The authors would like to express their sincere appreciation to the Endocrinology Clinic, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, for their full cooperation and support during data collection. The authors also acknowledge the statistician from the Faculty of Medicine, Universiti Kebangsaan Malaysia, for valuable assistance with the statistical analysis.

Informed Consent: Individual consent was waived due to the retrospective nature of the study. All data were anonymised prior to analysis to protect participant confidentiality.

Authors' Contributions: HST and IAB contributed to the conception and design of the study, including preparation of the research proposal. HST and IAB were responsible for data collection, management, and analysis. MMM and JAA provided critical supervision, methodological guidance, and validation of the analytical process. HST drafted the initial manuscript, and IAB, MMM, and JAA contributed to critical revision for important intellectual content. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflicts of Interest: The authors declare no conflict of interest.

REFERENCES

1. Hoogeveen EK. The epidemiology of diabetic kidney disease. Kidney Dial 2022;2(3):433-442.
2. Ministry of Health Malaysia. Clinical practice guidelines on management of type 2 diabetes mellitus. 6th ed. Malaysia: Ministry of Health Malaysia; 2020.
3. Akhtar S, Nasir JA, Ali A, *et al*. Prevalence of type 2 diabetes and prediabetes in Malaysia: a systematic review and meta-analysis. PLoS One 2022;17(1):e0263139.
4. Lazar S, Ionita I, Reurean-Pintilei D, *et al*. How to measure glycemic variability? A literature review. Medicina (Kaunas) 2023;60(1):61.
5. Breyton AE, Lambert-Porcheron S, Laville M, *et al*. CGMS and glycemic variability, relevance in clinical research to evaluate interventions in T2D: a literature review. Front Endocrinol (Lausanne) 2021;12:666008.
6. Xu S, Qin Z, Yuan R, *et al*. The hemoglobin glycation index predicts the risk of adverse cardiovascular events in coronary heart disease patients with type 2 diabetes mellitus. Front Cardiovasc Med 2022;9:992252.
7. Boye KS, Thieu VT, Lage MJ, *et al*. The association between sustained HbA1c control and long-term complications among individuals with type 2 diabetes: a retrospective study. Adv Ther 2022;39(5):2208-2221.
8. Wan KS, Hairi NN, Mustapha F, *et al*. Prevalence of diabetic kidney disease and the associated factors among patients with type 2 diabetes in a multi-ethnic Asian country. Sci Rep 2024;14(1):7074.
9. Wang J, Zhang L, Bai Y, *et al*. The influence of shorter red blood cell lifespan on the rate of HbA1c target achieved in type 2 diabetes patients with a HbA1c detection value lower than 7. J Diabetes 2023;15(1):7-14.
10. Xin S, Zhao X, Ding J, *et al*. Association between hemoglobin glycation index and diabetic kidney disease in type 2 diabetes mellitus in China: a cross-sectional inpatient study. Front Endocrinol (Lausanne) 2023;14:1108061.
11. Wei X, Chen X, Zhang Z, *et al*. Risk analysis of the association between different hemoglobin glycation index and poor prognosis in critical patients with coronary heart disease: a study based on the MIMIC-IV database. Cardiovasc Diabetol 2024;23(1):113.
12. MDCalc. CKD-EPI equations for glomerular filtration rate (GFR). Available from: https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr
13. Carette C, Czernichow S. Harms and benefits of the haemoglobin glycation index (HGI). Eur J Prev Cardiol 2017;24(13):1402-1404.
14. Joung HN, Kwon HS, Baek KH, *et al*. Consistency of the glycation gap with the hemoglobin glycation index derived from a continuous glucose monitoring system. Endocrinol Metab (Seoul) 2020;35(2):377-383.
15. Lin CH, Lai YC, Chang TJ, *et al*. Hemoglobin glycation index predicts renal function deterioration in patients with type 2 diabetes and a low risk of chronic kidney disease. Diabetes Res Clin Pract 2022;186:109834.
16. Nakasone Y, Miyakoshi T, Sakuma T, *et al*. Hemoglobin glycation index: a novel risk factor for incident chronic kidney disease in an apparently healthy population. J Clin Endocrinol Metab 2024;109(3):e1055-e1060.
17. Tatli E. Hemoglobin glycation index and triglyceride-glucose index are related to diabetic nephropathy. Cir Cir 2025;93(1):41-46.
18. Zhou W, Zhang L, Liu T. Association between the hemoglobin glycation index (HGI) and risk of diabetic nephropathy: a retrospective cohort study. Diabetes Metab Syndr Obes 2025;18:1859-1872.