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ORIGINAL RESEARCH

Association Between the Hemoglobin Glycation Index (HGI) and Risk of Diabetic Nephropathy: A Retrospective Cohort Study

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Background: The Hemoglobin Glycation Index (HGI) quantifies the difference between observed and predicted glycated hemoglobin (HbA1c) values, and has connections to multiple adverse outcomes. However, the relationship between HGI and the risk of diabetic nephropathy (DN) in patients with type 2 diabetes mellitus (T2DM) remains underexplored. The objective of this study was to examine the relationship between baseline HGI and the risk of DN development among patients with T2DM through a retrospective cohort study.

Methods: A single-center retrospective study was conducted on 1050 newly diagnosed T2DM patients with normal renal function at baseline. Participants were categorized into quartiles based on HGI values. The primary outcome was DN development, defined as persistent proteinuria or reduced estimated glomerular filtration rate (eGFR). Multivariable logistic regression, restricted cubic spline (RCS) analysis, and threshold effect models were employed to assess the association between HGI and DN risk. Subgroup and sensitivity analyses were conducted to validate the robustness of our findings, while mediation analysis was employed to explore potential underlying mechanisms.

Results: The study revealed a U-shaped relationship between HGI and DN risk. Both excessively low and high HGI levels were associated with an increased risk of DN, with the lowest risk observed at an HGI threshold of −0.648. In fully adjusted models, the highest HGI quartile (Q4) demonstrated a significantly increased risk of DN (OR = 1.54, 95% CI: 1.03–2.30, $P = 0.036$), while the lowest HGI quartile (Q1) also showed a trend toward higher risk (OR = 1.40, 95% CI: 0.92–2.14, $P = 0.115$). However, fasting plasma glucose (FPG) (P for overall = 0.217) and glycated hemoglobin (HbA1c) (P for overall = 0.529) did not show an association with the risk of DN. Subgroup and sensitive analyses confirmed the consistency of this U-shaped association across different patient demographics. Mediation analysis indicated that C-reactive protein (CRP) mediated 11.1% of the effect of |HGI| on DN.

Conclusion: In T2DM patients, baseline HGI exhibits a U-shaped association with DN risk, serving as a potential indicator for assessing DN risk.

Keywords: hemoglobin glycation index, diabetic nephropathy, retrospective cohort study

Introduction

The escalating global incidence of diabetes mellitus, fueled by an aging population, shifting lifestyles, and increasing obesity rates,[1] poses a significant challenge to public health systems. As per the most recent data from the International Diabetes Federation (IDF), the number of people with diabetes worldwide has already surpassed 460 million, with projections indicating a potential rise to nearly 800 million by 2045.[2]

Diabetic nephropathy (DN) represents one of the most devastating microvascular complications of diabetes and also ranks among the leading causes of end-stage renal disease (ESRD).[3] Its pathogenesis involves multiple interconnected pathways: chronic hyperglycemia induces oxidative stress through mitochondrial overproduction of reactive oxygen species (ROS), activates inflammatory cascades via NF-κB signaling, and stimulates the polyol pathway through aldose

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reductase overactivity.[4] These mechanisms collectively promote glomerular basement membrane thickening, mesangial matrix expansion, and podocyte injury, which in turn leads to progressive renal fibrosis.[5] In addition to renal dysfunction, DN also significantly increases cardiovascular risk through a number of mechanisms: hypertension is caused by the overactivation of the renin-angiotensin-aldosterone system (RAAS),[6] while atherosclerosis is accelerated by persistent inflammation and endothelial dysfunction.[7] This dual morbidity imposes profound quality-of-life and economic burdens.[3] Therefore, early intervention and delaying the onset and progression of diabetic nephropathy are of great importance.

Glycated hemoglobin (HbA1c) reflects mean blood glucose over 2–3 months and remains central to diabetes management.[8] Landmark trials like the DCCT and UKPDS have validated HbA1c's role in guiding treatment and preventing complications.[9,10] However, biological factors such as erythrocyte lifespan, glucose fluctuation patterns, and activity of glucose-metabolizing enzymes cause the HbA1c-glucose relationship—also known as the "glycation gap"—to vary significantly between individuals.[11,12] Mechanistically, aldose reductase in the polyol pathway simultaneously induces osmotic stress and promotes advanced glycation end-products (AGEs) formation,[13] while α-glucosidase-mediated carbohydrate digestion prolongs postprandial hyperglycemia and alters glycemic fluctuation patterns.[14] These distinct yet complementary mechanisms, operating independently of glycemic levels, collectively contribute to inter-individual variations in HbA1c levels. Consequently, the limitations of HbA1c highlight the necessity of implementing a quantitative metric to assess variations in HbA1c among individuals, enabling a more comprehensive and precise understanding of glucose metabolism among diabetic patients.

Given the limitations of HbA1c in reflecting individualized glycemic control, the Hempe research team innovatively proposed the Hemoglobin Glycation Index (HGI) in 2002.[15] This metric quantifies the deviation between measured HbA1c and its predicted value based on fasting blood glucose, enabling the specific assessment of individual hemoglobin glycation propensity independent of immediate glycemic levels. Prior studies have demonstrated significant associations between the HGI and various cardiometabolic diseases. Huang et al found that in populations with diabetic nephropathy, HGI independently predicted all-cause and cardiovascular mortality regardless of HbA1c levels.[16] Similarly, research by Wei and Cheng's teams established HGI as a prognostic marker for critical coronary artery disease and acute decompensated heart failure.[17,18] Regarding microvascular complications, HGI levels show well-documented correlations with the development and progression of diabetic peripheral neuropathy (DPN) and diabetic retinopathy (DR).[19,20] Notably, American Diabetes Association (ADA) research shows a strong link between HGI and AGEs, a well-known essential pathogenic mechanism of DN.[21] Building upon this evidence, we hypothesize that HGI may serve as a novel independent predictor for DN. This study aims to provide new evidence for early warning systems of DN and establish a theoretical foundation for developing precision intervention strategies, ultimately achieving the public health goal of reducing disease burden.

Methods and Materials

Participants

This study conducted a single-center retrospective analysis of 1050 patients newly diagnosed with type 2 diabetes mellitus (T2DM) at our hospital between January 1, 2009, and December 31, 2014. T2DM was defined according to the 2009 ADA Standards of Medical Care in Diabetes.[22] The main inclusion criteria were: (1) Age ≥ 18 years, (2) initial diagnosis of T2DM, and (3) normal renal function at baseline (eGFR ≥ 60mL/min/1.73m² & UACR < 30mg/g). The main exclusion criteria were: (1) Type 1 Diabetes Mellitus (T1DM) and other specific types of diabetes, (2) additional primary or secondary conditions that could result in renal insufficiency, (3) significant trauma, infections, and other stress-related states, (4) hepatitis, tuberculosis, malignancies, anemia, and pregnancy, and (5) incomplete clinical data. Figure S1 illustrates the detailed study flow.

Data Collection and Definition

Trained physicians collected information on patients' demographic characteristics, physiological parameters, laboratory tests, medical history, and discharge hypoglycemic medication from the electronic medical information record system. Body mass index (BMI) was defined as weight (kg) / (height [m]²). Hypertension was defined as a systolic blood pressure

(SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg, or the use of antihypertensive medications, or a previous diagnosis of hypertension. Smoking behavior was divided into two categories: never smokers, who had smoked fewer than 100 cigarettes in their lifetime, and smokers, who had smoked 100 or more cigarettes. The diagnosis of diabetic retinopathy, diabetic peripheral neuropathy, and diabetic peripheral angiopathy relied on a thorough evaluation by a qualified clinician utilizing fundus examination, electromyography, and color Doppler ultrasonography of the extremities, respectively.

After an overnight fast lasting at least 8 hours, peripheral venous blood samples were collected and various biochemical parameters were subsequently analyzed in the laboratory. These consist of ALB, BUN, SCr, UA, FPG, TC, TG, HDL-C, LDL-C, ApoA1, ApoB, and Lp(a). All other laboratory tests were gathered and examined promptly upon the patient's admission. The estimated glomerular filtration rate (eGFR) was calculated using the blood creatinine level according to the CKD-EPI formula.[23] A linear regression model was constructed based on the FPG and HbA1c data of all patients in this study. The model was used to calculate the predicted HbA1c values, with the specific formula being: Predicted HbA1c = 0.013 × FPG + 6.37. Subsequently, the predicted HbA1c value was subtracted from the observed HbA1c for each value to obtain the HGI (Figure 1).

Endpoints and Follow-up

The primary outcome of this study was the development of DN. According to the KDIGO 2021 guidelines, DN was defined as the presence of persistent proteinuria (UACR ≥ 30 mg/g) for a minimum of three months and/or an eGFR < 60 mL/min/1.73 m².[24]

Patients who took part in the study were followed up by telephone and/or annual outpatient visits until December 31, 2023.

Statistical Analysis

The Kolmogorov–Smirnov test was employed to assess the conformity of continuous variables to a normal distribution. (Table S1) Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range (IQR)). Categorical variables are presented as numbers (percentages).

Patients were categorized into four groups based on HGI quartiles: group Q1 (n=263, HGI < −1.283), group Q2 (n=262, −1.283 ≤ HGI < −0.228), group Q3 (n=262, −0.228 ≤ HGI < 1.147), and group Q4 (n=263, HGI ≥ 1.147).

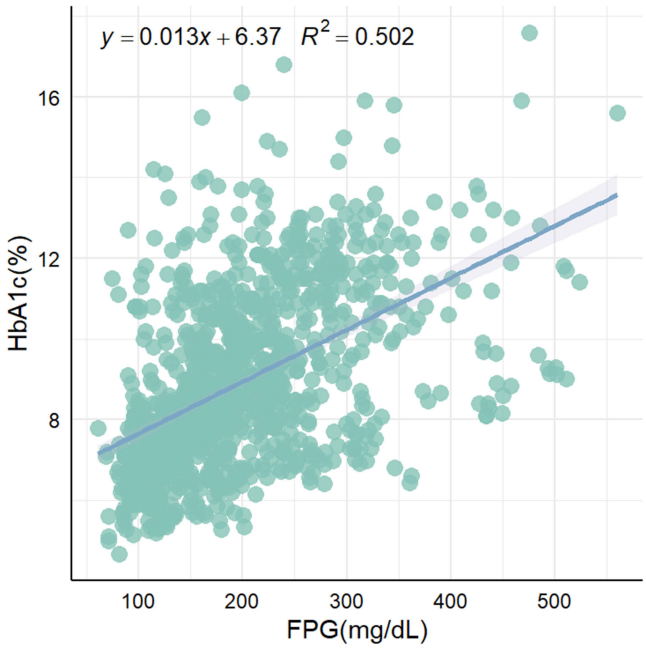

Figure 1 Linear regression model for HbA1c prediction.

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Continuous variables were compared between groups using analysis of variance (ANOVA) or the Kruskal–Wallis test. Categorical variables were compared between groups using the chi-square (χ^2) test (Table S2).

We first evaluated multicollinearity among variables using the generalized variance inflation factor (GVIF). As shown in Table S3, variables with $GVIF^{(1/(2Df))} > 2$ were excluded from subsequent analyses. The remaining variables ($GVIF^{(1/(2Df))} \leq 2$) were then subjected to both Boruta algorithm and Lasso regression analysis. The final variable set for Model 3 was determined by taking the intersection of results from these two methods (Figure 2).

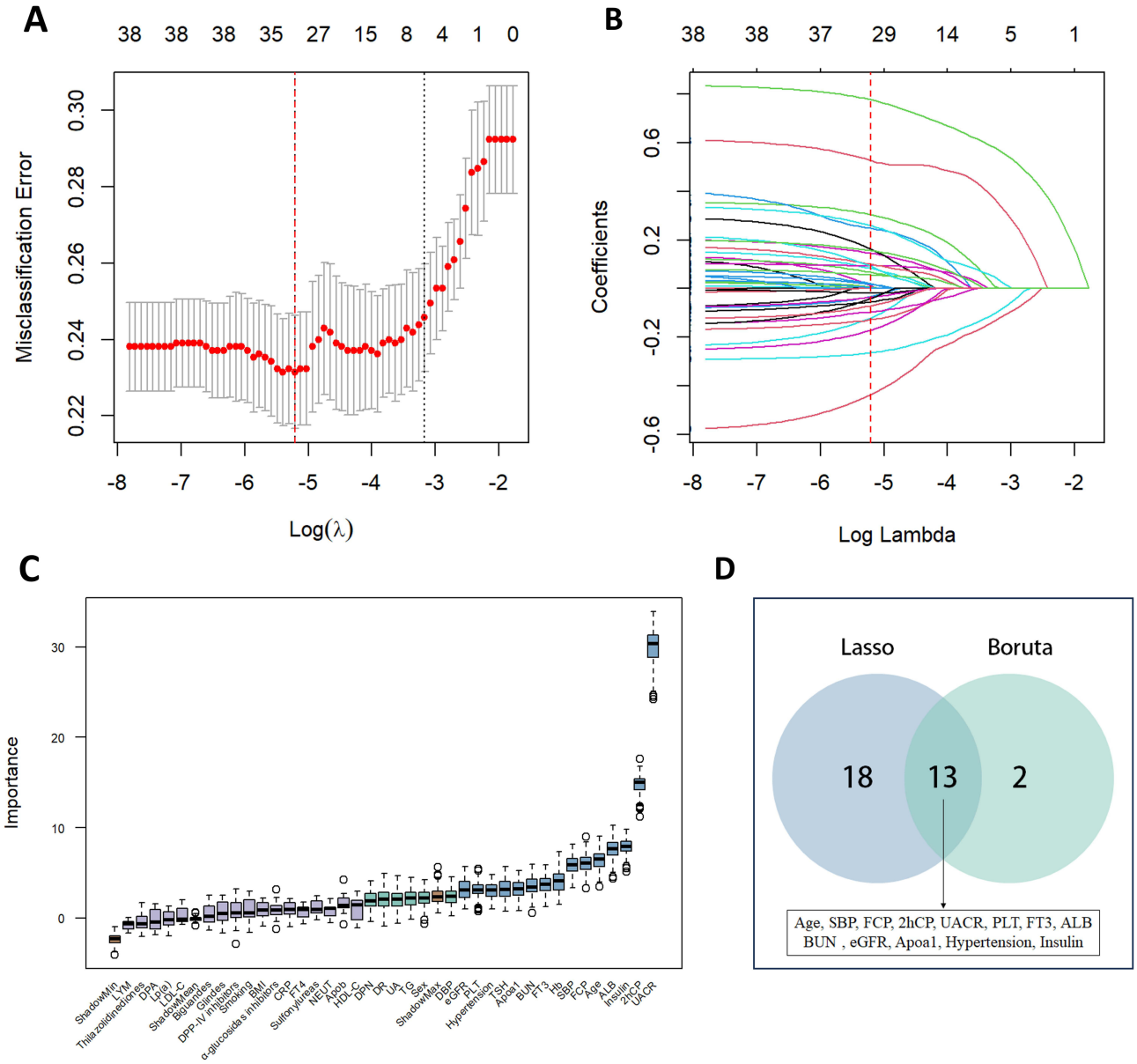

Figure 2 Covariate selection using Lasso and Boruta algorithms. (**A**) Misclassification error rate as a function of the regularization parameter λ (log scale). The red line indicates the optimal λ value selected based on the lowest misclassification error, and the gray bars represent the standard deviation of the error across different folds in cross-validation. (**B**) Path diagram showing the coefficients of the features as a function of the log of the regularization parameter λ. The vertical red line indicates the optimal λ value, where the most stable and significant features are retained. (**C**) Importance of features as determined by the Boruta algorithms. The boxplots represent the distribution of feature importance scores across different runs, highlighting the most influential predictors in the model. (**D**) Venn diagram comparing the features selected by Lasso and Boruta methods. The overlap (13 features) indicates the common features identified by both methods as important, while the unique features of each method are also shown (18 for Lasso, 2 for Boruta).

Three logistic regression models were constructed to assess the value of HGI as an independent predictor. Model 1 was unadjusted, Model 2 was adjusted for Age and Sex, and Model 3 was adjusted for Age, SBP, FCP, 2hCP, UACR, PLT, FT3, ALB, BUN, eGFR, Hypertension, Insulin, Apoa1. Odds ratios (OR) were calculated, and the results were presented as OR (95% CI). HGI was initially treated as a continuous variable and directly incorporated into the regression models to assess the effect of each unit change on the dependent variable. Then, to examine the impact of HGI at different levels, HGI was categorized into quartiles and incorporated into the regression model as a categorical variable, with the Q3 group as the reference. Additionally, trend regression analysis was performed by calculating the median values of each quartile of HGI and substituting these values for the original values in the model to assess the linear trend relationship between HGI and DN.

To explore the potential nonlinear relationships among HbA1c, FPG, and HGI with DN, a restricted cubic spline (RCS) model with four nodes at the 5th, 35th, 65th, and 95th percentiles of the relevant independent variables' distribution was constructed.

The likelihood method was used to estimate the optimal threshold for HGI by maximizing all potential values. Subsequently, a two-piecewise logistic regression analysis was conducted on either side of this threshold to explore the relationship between HGI and DN incidence. Furthermore, we employed the likelihood ratio test to evaluate the superiority of the segmented logistic regression model compared to a standard logistic regression model.

We conducted subgroup and sensitivity analyses to further validate our findings. For subgroup analysis, participants were stratified by clinically relevant factors including age, sex, BMI, history of hypertension, and smoking status, with potential interactions between these subgroups and HGI assessed using ANOVA. To ensure the robustness of our results, sensitivity analysis was performed by excluding outliers (defined as values beyond 1.5 times the IQR) and adjusting for all covariates in Model 3.

Furthermore, mediation analyses using the bootstrap method were conducted to assess the direct and indirect associations between the absolute value of HGI and the incidence of DN, with CRP as the mediating variable.

All data were analyzed using R version 4.5.0, and a two-sided $P < 0.05$ was considered statistically significant.

Results

General Patient Characteristics

The baseline characteristics of the cohort study participants (n=1050) categorized by outcome are listed in Table 1. The mean age of the participants was 54 years, and approximately 61% were male. Over an average follow-up period of 10.95 years, 307 participants were diagnosed with DN, comprising 245 individuals with persistent proteinuric DN, 16

Table 1 Baseline Characteristics According to Outcome

Group	Total (n = 1050)	Non-DN (n = 743)	DN (n = 307)	*P* value
Demographic characteristics				
Age (years)	54.00 (47.00, 61.00)	54.00 (47.00, 61.00)	57.00 (48.00, 64.50)	0.001*
Sex (male, %)	640 (61.0)	454 (61.1)	186 (60.6)	0.931
Smoking, n (%)	413 (39.3)	291 (39.2)	122 (39.7)	0.917
Physiological parameters				
BMI (kg/m^2)	24.74 (22.92, 26.66)	24.68 (22.86, 26.69)	24.77 (23.12, 26.57)	0.657
SBP (mmHg)	130.00 (120.00, 140.00)	130.00 (120.00, 139.00)	132.00 (124.00, 143.00)	<0.001*
DBP (mmHg)	80.00 (72.00, 85.00)	80.00 (72.00, 85.00)	80.00 (72.50, 86.00)	0.876
Laboratory tests				
FPG (mg/dL)	184.05 (134.28, 242.05)	176.22 (127.71, 232.47)	198.54 (152.64, 280.29)	<0.001*
HbA1c (%)	8.59 (7.20, 10.50)	8.30 (7.10, 10.01)	9.40 (7.60, 11.05)	<0.001*
FCP (ng/mL)	1.88 (1.28, 2.52)	1.91 (1.33, 2.52)	1.70 (1.13, 2.49)	0.016*
2hCP (ng/mL)	4.12 (2.55, 6.54)	4.51 (2.94, 7.14)	3.29 (2.12, 5.00)	<0.001*
WBC ($10^9/L$)	6.08 (5.10, 7.11)	6.09 (5.06, 7.11)	6.08 (5.16, 7.12)	0.703

(*Continued*)

Table 1 (Continued).

Group	Total (n = 1050)	Non-DN (n = 743)	DN (n = 307)	*P* value
NEUT (10^9/L)	3.56 (2.83, 4.30)	3.51 (2.78, 4.31)	3.60 (2.92, 4.30)	0.2
LYM (10^9/L)	1.90 (1.56, 2.39)	1.92 (1.56, 2.40)	1.89 (1.58, 2.35)	0.465
PLT (10^9/L)	191.00 (159.25, 229.75)	194.00 (162.00, 232.00)	188.00 (150.50, 222.70)	0.029*
Hb (g/L)	141.00 (130.00, 151.00)	141.00 (130.00, 151.00)	142.00 (127.50, 153.00)	0.966
CRP(mg/L)	1.50 (0.85, 2.18)	1.44 (0.81, 2.09)	1.65 (0.98, 2.30)	0.005*
ALB (g/L)	41.43 ± 4.04	41.84 ± 4.10	40.43 ± 3.71	<0.001*
BUN (mmol/L)	5.40 (4.60, 6.40)	5.40 (4.60, 6.30)	5.60 (4.70, 6.60)	0.03*
eGFR (mL/min/1.73m^2)	101.37 (91.80, 109.32)	102.00 (93.17, 109.68)	100.35 (89.98, 108.58)	0.092
UA (μmol/L)	282.20 (229.85, 335.88)	282.40 (230.52, 335.85)	282.00 (228.20, 336.07)	0.91
TC (mmol/L)	4.52 (3.93, 5.18)	4.49 (3.91, 5.20)	4.58 (3.98, 5.16)	0.192
TG (mmol/L)	1.62 (1.12, 2.41)	1.60 (1.10, 2.42)	1.66 (1.15, 2.41)	0.37
HDL-C (mmol/L)	1.10 (0.93, 1.32)	1.10 (0.93, 1.32)	1.10 (0.93, 1.32)	0.986
LDL-C (mmol/L)	2.52 (2.05, 3.01)	2.52 (2.04, 3.02)	2.52 (2.08, 3.00)	0.722
Apoa1 (g/L)	1.19 (1.04, 1.35)	1.20 (1.06, 1.35)	1.16 (1.02, 1.33)	0.036*
Apob (g/L)	0.88 (0.74, 1.04)	0.89 (0.75, 1.04)	0.87 (0.73, 1.02)	0.208
Lp(a) (g/L)	0.09 (0.05, 0.17)	0.09 (0.05, 0.17)	0.10 (0.05, 0.16)	0.378
UACR (mg/g)	8.85 (6.00, 13.70)	7.90 (5.50, 11.95)	12.70 (8.70, 19.45)	<0.001*
TSH (uIU/mL)	1.58 (1.00, 2.42)	1.65 (1.05, 2.51)	1.40 (0.88, 2.13)	<0.001*
FT3 (pmol/L)	4.50 (4.20, 4.90)	4.50 (4.20, 4.91)	4.56 (4.20, 4.88)	0.694
FT4 (pmol/L)	16.30 ± 2.46	16.24 ± 2.47	16.43 ± 2.43	0.266
Medical history				
Hypertension, n (%)	466 (44.4)	300 (40.4)	166 (54.1)	<0.001*
DR, n (%)	246 (23.4)	156 (21.0)	90 (29.3)	0.005*
DPN, n (%)	655 (62.4)	434 (58.4)	221 (72.0)	<0.001*
DPA, n (%)	523 (49.8)	358 (48.2)	165 (53.7)	0.116
Discharge hypoglycemic medication				
Insulin, n (%)	694 (66.1)	443 (59.6)	251 (81.8)	<0.001*
α-glucosidase inhibitors, n (%)	544 (51.8)	373 (50.2)	171 (55.7)	0.12
Thiazolidinediones, n (%)	181 (17.2)	134 (18.0)	47 (15.3)	0.33
Glinides, n (%)	189 (18.0)	135 (18.2)	54 (17.6)	0.893
Sulfonylureas, n (%)	193 (18.4)	144 (19.4)	49 (16.0)	0.225
Biguanides, n (%)	496 (47.2)	370 (49.8)	126 (41.0)	0.012*
DPP-IV inhibitors, n (%)	203 (19.3)	160 (21.5)	43 (14.0)	0.006*

Note: *$P < 0.05$.

Abbrevitions: DN, Diabetic Nephropathy; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; FPG, Fasting Plasma Glucose; HbA1c, Hemoglobin A1c; FCP, Fasting C-Peptide; 2hCP, 2-hour C-Peptide; WBC, White Blood Cell; NEUT, Neutrophil; LYM, Lymphocyte; PLT, Platelet; Hb, Hemoglobin; CRP, C-reactive protein; ALB, Albumin; BUN, Blood Urea Nitrogen; eGFR, Estimated Glomerular Filtration Rate; UA, Uric Acid; TC, Total Cholesterol; TG, Triglycerides; HDL-C, High-Density Lipoprotein; LDL-C, Low-Density Lipoprotein; Apoa1, Apolipoprotein A-I; Apob, Apolipoprotein B; Lp(a), Lipoprotein(a); UACR, Urine Albumin Creatinine Ratio; TSH, Thyroid Stimulating Hormone; FT3, Free Triiodothyronine; FT4, Free Thyroxine; DR, Diabetic Retinopathy; DPN, Diabetic Peripheral Neuropathy; DPA, Diabetic Peripheral Angiopathy.

individuals with eGFR-decreased DN, and 46 individuals with both characteristics. Individuals who developed DN were older and exhibited notably elevated SBP, FPG, HbA1c, CRP, BUN, and UACR levels. In contrast, they showed significantly reduced FCP, 2hCP, PLT, ALB, Apoa1, and TSH levels. Additionally, individuals who developed DN were more likely to have hypertension, diabetic retinopathy, and diabetic peripheral neuropathy compared to those who did not develop DN. Regarding discharge hypoglycemic medications, patients with DN had a higher proportion of insulin use, while the use of biguanides and DPP-IV inhibitors was lower compared to those without DN.

Association Between HGI and the Risk of Diabetic Nephropathy Development

Table 2 presents three logistic regression models designed to explore the relationship between HGI and DN. Initially, we incorporated HGI as a continuous variable within the models. In Models 1 and 2, a statistically significant positive association was observed between HGI and the incidence of DN (Model 1: OR = 1.10 (1.02–1.18), $P = 0.011$; Model 2:

Table 2 OR (95% CI) of Primary Outcome According to HGI in the Three Models

Variables	Model 1[a]		Model 2[b]		Model 3[c]	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
HGI continuous	1.10 (1.02–1.18)	0.011*	1.11 (1.03–1.19)	0.005*	1.00 (0.92–1.09)	0.955
HGI quartile						
Q1	0.94 (0.64–1.38)	0.749	0.93 (0.63–1.37)	0.718	1.40 (0.92–2.14)	0.115
Q2	0.79 (0.53–1.16)	0.232	0.78 (0.52–1.16)	0.217	1.18 (0.77–1.82)	0.435
Q3	Ref.		Ref.		Ref.	
Q4	1.56 (1.08–2.25)	0.018*	1.65 (1.14–2.40)	0.008*	1.54 (1.03–2.30)	0.036*
P for trend	0.002*		<0.001*		0.880	

Notes: *$P < 0.05$. [a]Model 1: Crude; [b]Model 2: adjusted for Age, Sex; [c]Model 3: adjusted for Age, SBP, FCP, 2hCP, UACR, PLT, FT3, ALB, BUN, eGFR, Apoa1, Hypertension, Insulin.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval; HGI, Hemoglobin Glycation Index; Ref, Reference.

OR = 1.11 (1.03–1.19), $P = 0.005$). However, after adjusting for more variables in Model 3, the association between HGI and DN was no longer statistically significant (OR = 1.00 (0.92–1.09), $P = 0.955$). To investigate the impact of HGI on the incidence of developing DN at different levels, we categorized HGI into quartiles for a more detailed analysis. In Model 1 and Model 2, when compared to the Q3 group, the Q1 group (Model 1: OR = 0.94 (0.64–1.38), $P = 0.749$; Model 2: OR = 0.93 (0.63–1.37), $P = 0.718$) and the Q2 group (Model 1: OR = 0.79 (0.53–1.16), $P = 0.232$; Model 2: OR = 0.78 (0.52–1.16), $P = 0.217$) showed a reduced but not statistically significant risk of DN development. In contrast, the Q4 group (Model 1: OR = 1.56 (1.08–2.25), $P = 0.018$; Model 2: OR = 1.65 (1.14–2.40), $P = 0.008$) demonstrated a significantly higher risk of DN development. After adjusting for more variables in model 3, group Q3 was identified as having the lowest morbidity risk. Moreover, the incidence of DN was found to be increased in groups Q1 (OR = 1.40 (0.92–2.14), $P = 0.115$) and Q2 (OR = 1.18 (0.77–1.82), $P = 0.435$). Meanwhile, the Q4 group (OR = 1.54 (1.03–2.30), $P = 0.036$) still exhibited the highest risk of DN development among the four groups, which was statistically significant. Furthermore, we conducted trend tests in Model 3, which did not detect a statistically significant linear association between HGI and DN incidence risk (P for trend = 0.880).

The Detection of Nonlinear Relationships

Given that earlier models indicated a potential nonlinear relationship between HGI and the risk of DN development, we employed an RCS curve to delve deeper into the correlation between the two variables and assessed its modeling effects compared to FPG and HbA1c. As illustrated in Figure 3A–C, three models demonstrated consistent results, indicating that HGI exhibited a U-shaped correlation with the risk of DN development (P for nonlinear < 0.05). Regarding FPG and HbA1c, as illustrated in Figure 3D–I, models 1 and 2 demonstrated a linear relationship between the two variables and DN (P for nonlinear > 0.05), which was no longer significant after adjusting for additional variables in model 3 (P for overall > 0.05).

As shown in Table 3, based on the two-piecewise logistic regression model, we determined the HGI value corresponding to the lowest risk point as −0.648 (P for the log-likelihood ratio test < 0.001). When the HGI level was below the threshold, each unit increase in HGI was associated with a 35% reduction in the risk of developing DN (OR = 0.65 (0.48–0.88), $P = 0.006$). As HGI increased to the threshold, the risk of DN development reached its lowest level. However, when the HGI level exceeded the threshold, HGI became significantly positively correlated with the risk of DN development, with each unit increase in HGI leading to a 12% increase in the risk of DN (OR = 1.12 (1.02–1.28), $P = 0.044$).

Subgroup Analysis and Sensitivity Analysis

The subgroup analysis indicated that the relationship between HGI quartiles and the risk of DN development showed generally consistent trends across subgroups categorized by age, sex, BMI, history of hypertension, and smoking history, with most demonstrating U-shaped associations (Figure 4). Additionally, there was no observed interaction between HGI and the stratification variables (P for interaction > 0.05). To further validate the robustness of our findings, we conducted

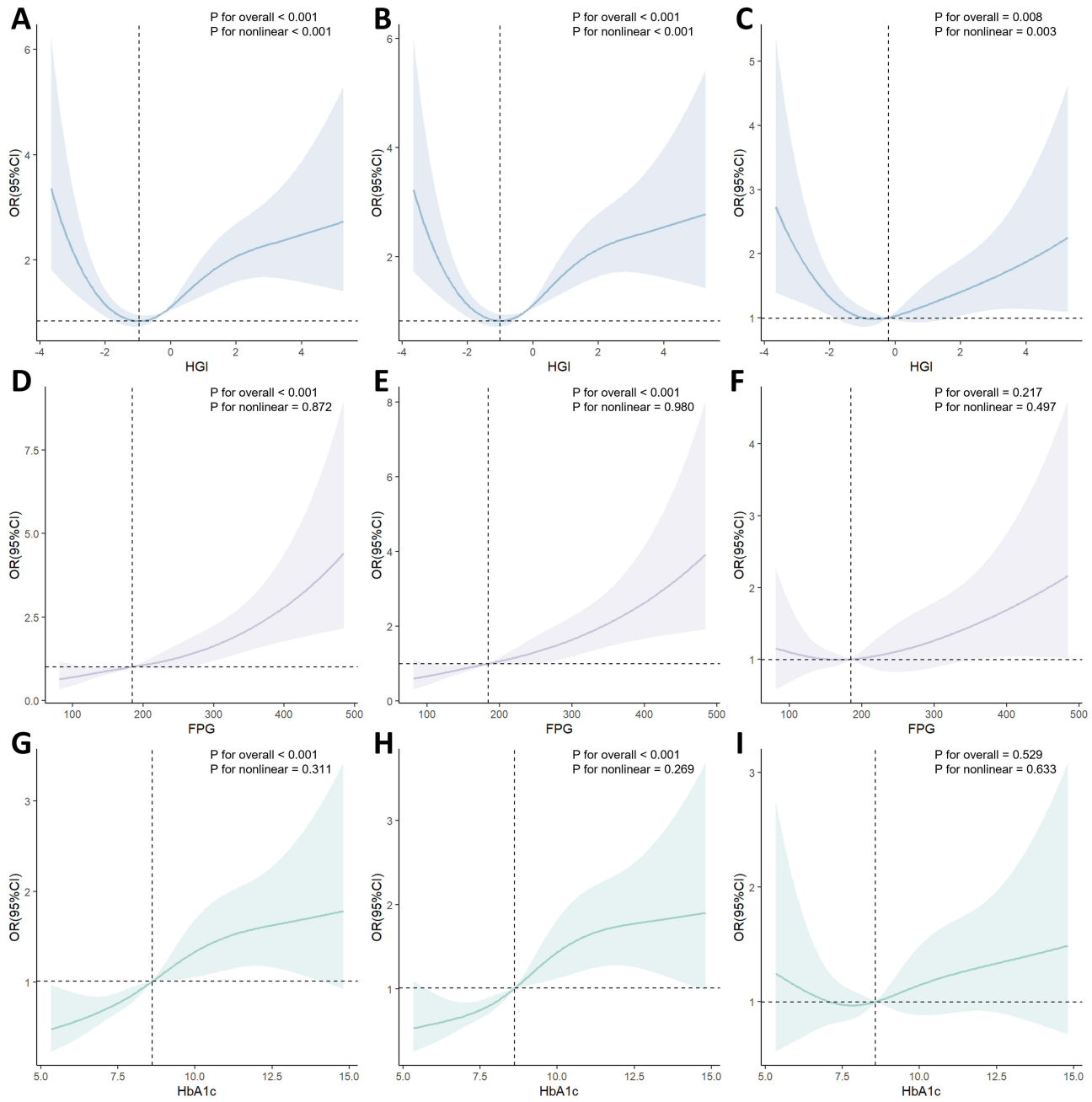

Figure 3 Restricted cubic spline analysis of glycemic indicators and diabetic nephropathy risk. (**A–C**) The association between HGI and diabetic nephropathy risk from Model 1 to Model 3, is represented as odds ratios (OR) with 95% confidence intervals (CIs). (**D–F**) The association between FPG and diabetic nephropathy risk from Model 1 to Model 3, is represented as odds ratios (OR) with 95% confidence intervals (CIs). (**G–I**) The association between HbA1c and diabetic nephropathy risk from Model 1 to Model 3, is represented as odds ratios (OR) with 95% confidence intervals (CIs). The solid line indicates the OR and the shaded area represents the 95% CI.

sensitivity analyses. Using 1.5 times the IQR as the cutoff value, we excluded 15 patients (1.43%) with outlier HGI values. As shown in Figure S2, after adjustment for all covariates in Model 3, the results remained highly consistent, demonstrating the stability of our primary conclusions.

Mediation Analysis

Lastly, we conducted mediation analyses using the absolute value of HGI as the predictor variable, baseline CRP as the mediator variable, and DN as the outcome variable. Figure 5 illustrates the mediating role of CRP in the relationship

Table 3 Threshold Effect Analyses of HGI on the Risk of DN in Patients with T2DM

	OR (95% CI)	*P*
Fitting model by standard logistics regression	1.00 (0.92–1.09)	0.955
Fitting model by two-piecewise logistics regression		
Infection point (K)	−0.648	
≤K	0.65 (0.48–0.88)	0.006
>K	1.12 (1.02–1.28)	0.044
P for the log-likelihood ratio test	<0.001	

Notes: Adjusted for Age, SBP, FCP, 2hCP, UACR, PLT, FT3, ALB, BUN, eGFR, Apoa1, Hypertension, Insulin;
Abbreviations: DN, Diabetic Nephropathy; T2DM, Type 2 Diabetes Mellitus; OR, Odds Ratio; HGI, Hemoglobin Glycation Index.

between HGI and DN. The results indicated a significant positive correlation between the absolute value of HGI and the onset of DN, and baseline CRP mediated 11.1% of the indirect effects of DN.

Discussion

In this retrospective study, we explored for the first time the association between HGI and the risk of DN development in patients with T2DM. The results indicate that both excessively low and excessively high HGI levels correlate with a heightened risk of developing DN. This relationship persisted strongly even after accounting for various confounding factors. The results from the RCS curve analysis indicate a U-shaped relationship between HGI and DN. Threshold analysis enabled us to pinpoint the lowest point of risk associated with the development of DN. Subgroup analyses demonstrated that this U-shaped association remained consistent across different subgroups, with no significant interaction observed between HGI and the stratification variables, and sensitivity analyses further confirmed the robustness of these primary findings. The analysis of mediating effects confirmed the link between elevated absolute values of HGI and a heightened risk of DN development, highlighting the significant mediating role of CRP in this relationship.

In previous studies, it has been indicated that HGI can serve as an independent predictor of impaired renal function. For example, a prior 10-year cohort study carried out in Korea suggested that elevated HGI correlated with a heightened risk of chronic kidney disease (CKD) in diabetic patients, whether they had received standardized glycemic control therapy. Furthermore, individuals with higher HGI exhibited greater susceptibility to developing CKD, even when their HbA1c levels were comparable.[25] Similarly, Nakasone et al's research involving a healthy population indicated that HGI is an emerging risk factor for CKD.[26] In the context of acute kidney injury (AKI), HGI also demonstrates a distinctive predictive capability. A study carried out by Chen et al revealed that elevated absolute value of HGI levels are significantly associated with an increased incidence of contrast-associated acute kidney injury (CI-AKI) in patients undergoing coronary angiography (CAG) and percutaneous coronary intervention (PCI), which is similar to the results we obtained.[27] Nonetheless, some studies have arrived at a contrasting conclusion. A recent study by Cardoso et al indicated that HGI did not show greater predictive efficacy compared to HbA1c in patients with T2DM, particularly regarding the prediction of new-onset microproteinuria, macroalbuminuria, or the progression of renal function, and that HGI did not offer any additional benefit.[19] We speculate that the smaller sample size, the severity of the patient's conditions, racial differences among the study subjects, and the shorter follow-up duration may be the reasons for the discrepancies in the study conclusions.

The precise mechanisms underlying the U-shaped relationship between HGI and DN remain incompletely elucidated. Several potential pathways may account for the increased risk of DN associated with elevated HGI. Firstly, elevated HGI levels indicate accelerated non-enzymatic glycation, leading to increased AGEs generation.[28] The progressive accumulation of AGEs in renal tissues induces basement membrane thickening and extracellular matrix deposition, thereby compromising normal renal function.[29] Secondly, elevated HGI not only upregulates pro-inflammatory cytokines such as TNF-α and CRP,[30,31] but these inflammatory mediators also directly contribute to glomerulosclerosis and interstitial fibrosis by activating mesangial cell proliferation, promoting inflammatory cell infiltration, and stimulating extracellular matrix

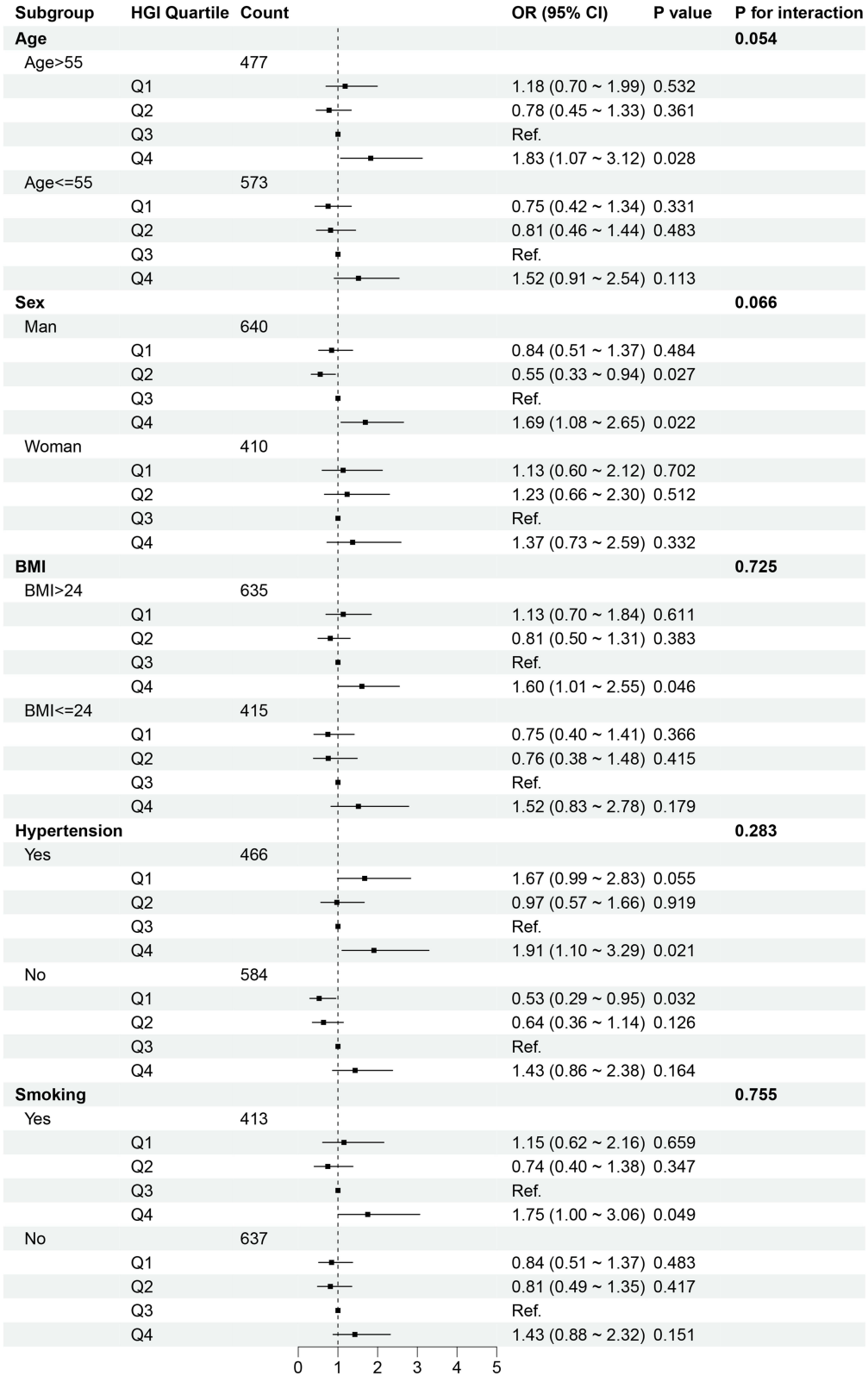

Figure 4 Subgroup analysis of HGI and risk of diabetic nephropathy.

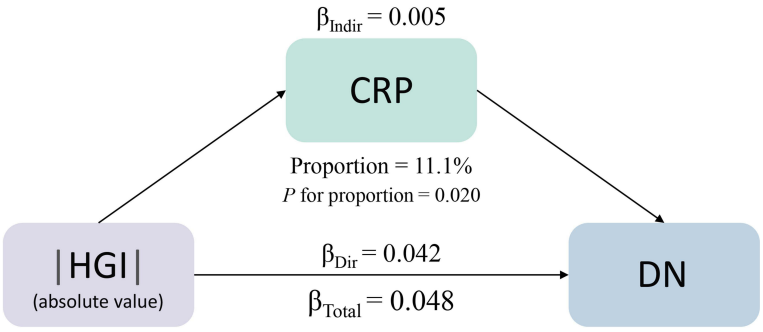

Figure 5 Mediation effects of HGI and CRP on diabetic nephropathy.

deposition.[5,32] Concurrently, HGI-associated oxidative stress damages podocytes and impairs the integrity of the glomerular filtration barrier.[33] Furthermore, elevated HGI often indicates that HbA1c levels overestimate actual blood glucose concentrations, potentially leading to excessive use of glucose-lowering medications and consequent hypoglycemia risk.[34] Importantly, hypoglycemia triggers sympathetic activation and vasoconstriction, resulting in decreased renal blood flow. In T2DM patients, recurrent hypoglycemic episodes may exacerbate renal function deterioration through these hemodynamic alterations.[35,36] Conversely, low HGI reflects distinct yet equally detrimental pathophysiological mechanisms. Primarily, low HGI may indicate a chronic stress-induced hyperglycemic state,[34,37] where surges in cortisol and catecholamines not only significantly elevate FPG but also induce glomerular hyperfiltration and mechanical endothelial injury.[38,39] Secondly, studies demonstrate that diabetic patients may develop anemia during the early compensatory phase of DN due to impaired iron metabolism and reduced erythropoietin production.[40] The consequent reduction in erythropoiesis shortens the HbA1c half-life, thereby masking persistent hyperglycemia. This occult hyperglycemic state promotes AGEs formation while inducing oxidative stress.[41] Notably, whether HGI is elevated or reduced, abnormal HGI levels can activate inflammatory signaling pathways, triggering excessive secretion of inflammatory factors including CRP. This sustained pro-inflammatory microenvironment not only exacerbates tissue damage but also actively drives disease progression. Our mediation analyses provide robust evidence supporting these pathophysiological mechanisms.

This study provides the first demonstration of a U-shaped association between HGI and DN risk in patients with T2DM, although several methodological limitations should be acknowledged. First, as a single-center observational study, causal inference is inherently limited despite rigorous multivariate adjustments and comprehensive sensitivity analyses. Residual confounding may persist due to unmeasured variables including dietary patterns, socioeconomic status, and diabetes duration. Second, the analysis was restricted to baseline HGI measurements, thereby precluding the assessment of longitudinal HGI variations' prognostic value. Additionally, the lack of other inflammatory biomarkers (e.g., TNF-α, IL-6) and continuous glucose monitoring data (e.g., mean amplitude of glycemic excursions [MAGE], continuous overlapping net glycemic action [CONGA]) limited both mechanistic exploration and comparative analyses with established glycemic variability indices. Lastly, the absence of experimental validation through animal models or in vitro systems represents a critical gap in verifying the proposed mechanisms involving AGEs accumulation and inflammatory cascade activation. Future multicenter prospective studies incorporating these experimental approaches are warranted to validate and extend our findings.

Conclusion

The results indicate that HGI is a novel instrument for forecasting the risk of DN progression in individuals with T2DM and that the relationship between HGI and the risk of development exhibits a nonlinear pattern. Consequently, evaluating patients' HGI could serve as an effective method for determining their risk of developing DN. Future studies should investigate whether interventions targeting HGI can improve the prognosis of these patients.

Abbreviations

2hCP, 2-hour postprandial C-peptide; ADA, American Diabetes Association; AGEs, Advanced Glycation End-products; AKI, Acute Kidney Injury; ALB, Albumin; ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; BMI, Body Mass Index; BUN, Blood Urea Nitrogen; CAG, Coronary Angiography; CI-AKI, Contrast-Induced Acute Kidney Injury; CKD, Chronic Kidney Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CONGA, Continuous Overlapping Net Glycemic Action; CRP, C-Reactive Protein; DBP, Diastolic Blood Pressure; DCCT, Diabetes Control and Complications Trial; Df, Degrees of freedom; DN, Diabetic Nephropathy; DPN, Diabetic Peripheral Neuropathy; DPP-IV, Dipeptidyl Peptidase-4; DR, Diabetic Retinopathy; eGFR, Estimated Glomerular Filtration Rate; ESRD, End-Stage Renal Disease; FCP, Fasting C-peptide; FT3, Free Triiodothyronine; FPG, Fasting Plasma Glucose; GVIF, Generalized Variance Inflation Factor;; HbA1c, Glycated Hemoglobin; HGI, Hemoglobin Glycation Index; HDL-C, High-Density Lipoprotein Cholesterol; IDF, International Diabetes Federation; IL-6, Interleukin-6; IQR, Interquartile Range; KDIGO, Kidney Disease, Improving Global Outcomes; LDL-C, Low-Density Lipoprotein Cholesterol; Lp(a), Lipoprotein(a); MAGE, Mean Amplitude of Glycemic Excursions; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; OR, Odds Ratio; PCI, Percutaneous Coronary Intervention; PLT, Platelet Count; RAAS, Renin-Angiotensin-Aldosterone System; RCS, Restricted Cubic Spline; ROS, Reactive Oxygen Species; SBP, Systolic Blood Pressure; SCr, Serum Creatinine; SD, Standard Deviation; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; TC, Total Cholesterol; TG, Triglycerides; TNF-α, Tumor Necrosis Factor-Alpha; TSH, Thyroid-Stimulating Hormone; UA, Uric Acid; UACR, Urine Albumin-to-Creatinine Ratio; UKPDS, United Kingdom Prospective Diabetes Study.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The research received approval from the Ethics Committee of The Affiliated Changzhou Second People's Hospital of Nanjing Medical University under Grant No. (2024-KY209-01) and was executed in compliance with the principles of the Declaration of Helsinki. Given the observational and retrospective nature of this study, the requirement for patient informed consent was waived by the Ethics Committee. All patient data were handled in strict compliance with confidentiality protocols.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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