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The effects of glycated hemoglobin and body mass index on the relationship between the hemoglobin glycation index and the hypoglycemia risk: a moderated mediation analysis

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Abstract

Aim: To explore the relationship between the hemoglobin glycation index (HGI) and the hypoglycemia risk, and the potential effect of glycosylated hemoglobin (HbA1c) and body mass index (BMI) on this relationship.

Methods: This is a prospective observational study. A total of 1,203 type 2 diabetes mellitus (T2DM) patients were included. Linear regression was used to establish an equation for calculating the HGI. Logistic regression models were employed to explore the association between the HGI and hypoglycemia. A moderated mediation approach was taken to detect the effect of BMI and HbA1c on the association between HGI and hypoglycemia.

Results: During the follow-up period (median 34.73 months), 344 patients developed hypoglycemia. The relationship between the HGI and hypoglycemia was significant [odds ratio (OR), 95% confidence interval (CI): 1.255 (1.089-1.446), $P = 0.001$] after adjusting for potential confounders. Compared to the low-HGI group, the risk of hypoglycemia in the high-HGI group was significantly elevated [OR (95%CI) = 1.603 (1.167-2.201), $P = 0.006$]. Trend tests suggested that the risk of hypoglycemia increased significantly from the low- to the high-HGI groups ($P = 0.003$). A significant mediation effect of HbA1c was observed along the path HGI \rightarrow Hypoglycemia (coefficient =



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0.128, 95%CI: 0.140-0.247, $P = 0.008$) and a significant moderation effect of BMI was observed along the path $HGI \rightarrow HGI \times BMI \rightarrow HbA1c$ (coefficient = 0.019, 95%CI: 0.004-0.040, $P = 0.022$), suggesting that HbA1c served as a mediator and BMI as a moderator of the relationship between the HGI and hypoglycemia.

Conclusion: The HGI was significantly associated with the risk of hypoglycemia in T2DM subjects. Moderated mediation analysis demonstrated that the association between the HGI and hypoglycemia was mediated by HbA1c and moderated by BMI. Interventions targeting HbA1c and BMI may mitigate the risk of hypoglycemia in T2DM patients.

Keywords: Hemoglobin glycation index, hypoglycemia, HbA1c, BMI, mediation, prospective study

INTRODUCTION

Hypoglycemia is a serious acute complication of diabetes^[1]. In type 2 diabetes mellitus (T2DM) patients receiving intensive hypoglycemic treatments, hypoglycemia is more common and the symptoms more serious than in other patients^[2]. Hypoglycemia not only renders it difficult to control the blood glucose level but is also closely related to diabetic vascular complications. Glycosylated hemoglobin (HbA1c) is an indicator of blood glucose metabolism. However, only about 60%-80% of the variation in HbA1c levels can be explained by the mean blood glucose level^[3]. The hemoglobin glycation index (HGI) has emerged as a metric to capture interindividual variation in HbA1c beyond mean glucose levels, reflecting differences in hemoglobin glycation propensity^[4,5]. Previous large-scale studies, including ACCORD, ADVANCE, and AleCardio, have linked HGI to both microvascular and macrovascular complications, as well as hypoglycemia risk^[6,7]. However, these studies often did not evaluate potential intermediating or moderating metabolic factors in the HGI-hypoglycemia pathway. In particular, insulin resistance - commonly estimated by the homeostatic model assessment for insulin resistance (HOMA-IR) - may influence both HbA1c levels and hypoglycemia susceptibility^[8,9], yet few studies have considered its potential confounding or mediating role. In addition, anthropometric indices such as body mass index (BMI) may interact with HGI through their impact on glucose-insulin dynamics, further modifying hypoglycemia risk. Addressing these gaps may improve individualized hypoglycemia risk prediction and inform targeted interventions.

METHODS

Study population

The study design has been described previously^[10]. In 2010, Ning *et al.* initiated a longitudinal, prospective cohort study in China - the Risk Evaluation of Cancers in Chinese Diabetic Individuals (REACTION) study - to investigate relationships between cancer, diabetes, and diabetes-related risk factors^[10]. A total of 1,837 T2DM patients from eight Beijing communities (Lugu, Babaoshan, Laoshan, Bajiao, Gucheng, Pingguoyuan, Jinding, and Guangning) were recruited. After excluding 192 individuals with a history of severe hypoglycemia, 1,645 remained under observation until 2011. Subsequently, 265 participants with missing data and 177 lost to follow-up were excluded, leaving 1,203 individuals for the final analysis in 2015 [Figure 1]. All participants provided written informed consent, and the study was approved by the Ethics Committee of Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine. The trial was registered at ClinicalTrials.gov (NCT01506869).

Questionnaires

All participants completed standardized questionnaires assessing disease history and antidiabetic treatments:

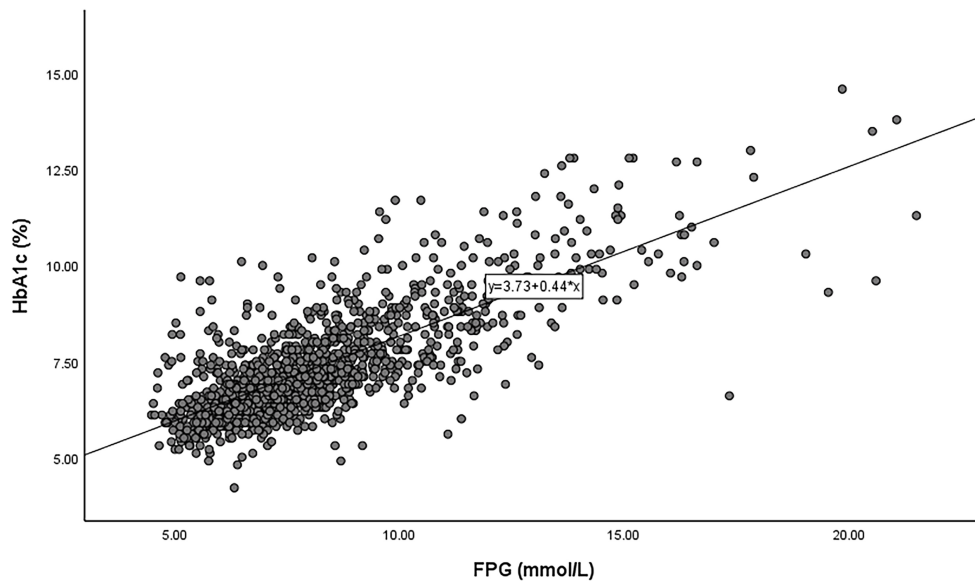


Figure 1. The HGI equation derived via linear regression. Predicted HbA1c level = $0.44 \times \text{FBG (mmol/L)} + 3.73$. The line represents the linear regression. HGI: Hemoglobin glycation index; FBG: fasting blood glucose; HbA1c: glycated hemoglobin.

- (1) T2DM: Defined as a self-reported history of T2DM, fasting blood glucose (FBG) ≥ 7.0 mmol/L, 2-h postprandial glucose (2hPG) ≥ 11.1 mmol/L, or HbA1c $\geq 6.5\%$ ^[11].
- (2) T2DM treatment: Intensive treatment was defined as either short-acting insulin (before meals) combined with long-acting insulin (before sleep) or use of an insulin pump. The use of diet and/or exercise alone was also recorded. Oral antidiabetic drugs included sulfonylureas, metformin, and acarbose.
- (3) Hyperlipemia: Defined as serum total cholesterol (TC) > 5.17 mmol/L or triglycerides (TGs) > 2.3 mmol/L^[12].
- (4) Coronary heart disease (CHD): Diagnosed based on typical symptoms, imaging, electrocardiography, and biochemical markers of myocardial damage^[13].
- (5) Hypertension: Defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, or a self-reported history of hypertension^[14].
- (6) Nonalcoholic fatty liver disease (NAFLD): Diagnosed based on serum biomarkers and ultrasonography.
- (7) Family history of T2DM: Positive if an immediate family member had been diagnosed with T2DM.
- (8) Smoking history: Defined as smoking at least one cigarette daily for ≥ 6 months.
- (9) Alcohol consumption: Defined as an average intake ≥ 50 g/day.

Measurements

Height, weight, BMI, and blood pressure were measured. Height was recorded barefoot to the nearest 0.01 m, and weight was measured in light clothing to the nearest 0.1 kg. BMI was calculated as weight (kg)/height (m²). Blood pressure was measured three times at 1-min intervals in the seated position using an electronic device, and the mean value was used for analysis. Laboratory measurements included serum TC, TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine, fasting plasma glucose (FPG), 2hPG, and HbA1c.

HGI

The linear regression model for predicting HbA1c included FBG as the sole independent variable, consistent with the definition by Hempe *et al.*^[6]. Other variables were not incorporated, and erythrocyte turnover-related indicators (e.g., ferritin, erythropoietin, reticulocyte count) were unavailable in our dataset.

Baseline FBG and HbA1c were used to establish their linear correlation [Figure 2]. A scatterplot was drawn with FBG on the x-axis and HbA1c on the y-axis. Linear regression yielded the following equation: predicted HbA1c = $0.44 \times \text{FBG (mmol/L)} + 3.73$ ($R^2 = 0.60$; $P < 0.001$). The HGI for each subject was calculated as: $\text{HGI} = \text{observed HbA1c} - \text{predicted HbA1c}$ ^[14].

Adjusted for Age, sex, Dyslipidemia, Hypertension, family history of T2DM, NAFLD, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), TC, LDL-C, DBP, and T2DM duration.

Outcome

The primary outcome was the first occurrence of hypoglycemia during follow-up. Hypoglycemia was defined as self-monitored blood glucose ≤ 3.9 mmol/L accompanied by symptoms requiring medical care or assistance from others. Symptoms included:

- (1) Autonomic symptoms: Hunger, fatigue, paleness, anxiety, tremor, tachycardia.
- (2) Central nervous system symptoms: Sweating, dizziness, blurred vision, impaired consciousness.

Statistical analysis

Continuous variables were presented as means \pm SDs or medians with interquartile ranges (25th-75th percentiles). Between-group comparisons were performed using the Student's *t*-test or one-way ANOVA for normally distributed variables, and the Mann-Whitney *U* test or Kruskal-Wallis test otherwise. Categorical variables were expressed as frequencies (percentages) and compared using the chi-squared test. Binary logistic regression was used to assess associations between HGI and hypoglycemia. The multivariate model was adjusted for age, sex, hyperlipidemia, hypertension, family history of T2DM, NAFLD, ALT, AST, GGT, TC, LDL-C, DBP, and T2DM duration (Model 1). The fully adjusted model additionally included TG, creatinine, systolic blood pressure (SBP), CAD history, pulse, tumor history, smoking, and alcohol consumption (Model 2). A moderated mediation analysis was performed to test whether the association between HGI and hypoglycemia was mediated by HbA1c and moderated by BMI. This analysis was specified using two regression equations: (1) $\text{HbA1c} = \beta_1 \times \text{HGI} + \beta_2 \times \text{BMI} + \beta_3 \times (\text{HGI} \times \text{BMI}) + \epsilon_1$; (2) $\text{Hypoglycemia} = \beta_4 \times \text{HGI} + \beta_5 \times \text{HbA1c} + \epsilon_2$. If moderation was significant, a simple slope analysis was conducted to analyze the HGI-hyperglycemia association at different BMI levels (Mean - 1 SD, Mean, Mean + 1 SD)^[15]. All continuous variables were mean-centered prior to analysis. The moderated mediation analysis was performed using PROCESS v4.0 (Model 7) in SPSS v26.0 (IBM Corp., Armonk, NY, USA). A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

For the descriptive analysis of baseline characteristics, HGI values were initially divided into quintiles to enable a more detailed comparison of demographic and clinical variables. For the analysis of hypoglycemia risk, tertiles (low, moderate, high HGI) were used to ensure adequate event counts per group and to facilitate interpretation of risk estimates. This approach was chosen a priori to balance statistical power with clinical interpretability.

Baseline characteristics

A total of 1,203 patients with T2DM were included in the analysis. The median follow-up duration was 34.73 months. During this period, 344 patients developed hypoglycemia. Based on HGI values, patients were divided into three groups: low-HGI, moderate-HGI, and high-HGI. Baseline characteristics - including BMI, duration of T2DM, FBG and 2hPG, HbA1c, GGT, creatinine, HDL-C, SBP, pulse, intensive

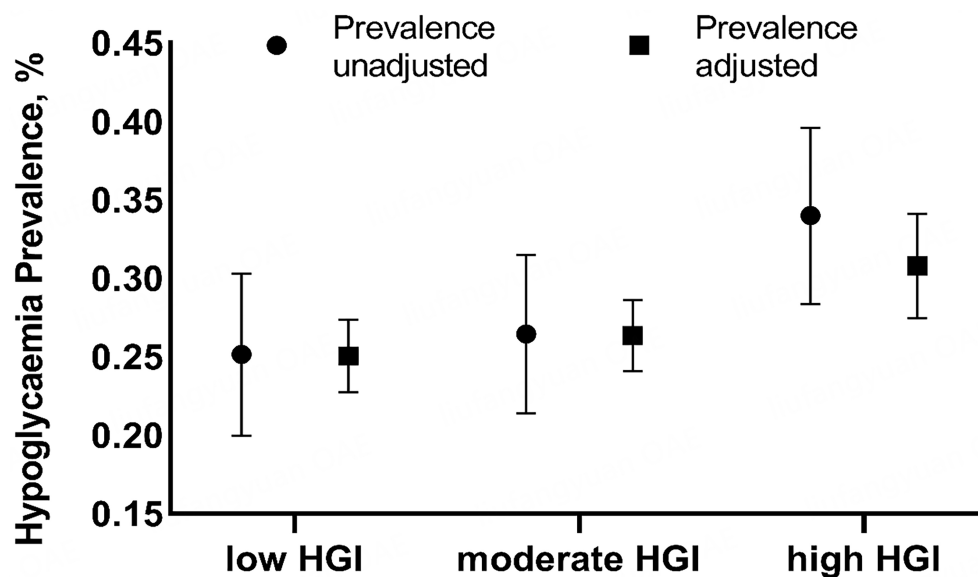


Figure 2. Unadjusted and adjusted prevalence of hypoglycemia. HGI: Hemoglobin glycation index.

treatment, sulfonylurea and insulin use, and alcohol consumption - differed significantly across groups [Table 1]. Figure 1 shows that the prevalence of hypoglycemia increased progressively from the low- to the high-HGI group. After adjusting for age, sex, hyperlipemia, hypertension, family history of T2DM, NAFLD, ALT, AST, GGT, TC, LDL-C levels, DBP, and duration of T2DM, the prevalence of hypoglycemia was 25.03% [95% confidence interval (CI) 22.73%-27.33%] in the low-HGI group, 26.34% (24.08%-28.61%) in the moderate-HGI group, and 30.78% (27.46%-34.10%) in the high-HGI group.

Relationship between HGI and hypoglycemia risk

Table 2 shows the association between HGI and hypoglycemia. When analyzed as a continuous variable, HGI was significantly associated with hypoglycemia [odds ratio (OR) (95%CI) = 1.242 (1.083-1.425), $P = 0.005$]. The risk of hypoglycemia in the high-HGI group was significantly higher than in the low-HGI group [OR (95%CI) = 1.534 (1.130-2.082), $P = 0.006$]. After full adjustment for age, sex, hyperlipemia, hypertension, family history of T2DM, NAFLD, ALT, AST, GGT, TC, LDL-C levels, DBP, duration of T2DM, TG and creatinine levels, SBP, CAD history, pulse, tumor history, and smoking and alcohol consumption, the relationship between HGI and hypoglycemia remained significant [OR (95%CI) = 1.255 (1.089-1.446), $P = 0.001$]. Similarly, the risk of hypoglycemia in the high-HGI group remained greater than that in the low-HGI group [OR (95%CI) = 1.603 (1.167-2.201), $P = 0.006$]. Trend analyses indicated that the risk of hypoglycemia increased progressively across HGI categories, from low to high, in both Model 1 ($P = 0.004$) and Model 2 ($P = 0.003$).

Mediation by HbA1c in the association between HGI and hypoglycemia

Table 3 presents the results of the mediation analysis. The path HGI → HbA1c indicated a significant direct effect of HGI on HbA1c (coefficient = 1.027, 95%CI 0.960-1.093, $P < 0.001$). The path HbA1c → Hypoglycemia suggested that HbA1c had a significant direct effect on hypoglycemia (coefficient = 0.125, 95%CI: 0.013-0.236, $P = 0.020$). The indirect path HGI → HbA1c → Hypoglycemia showed a significant mediation effect of HbA1c on the association between HGI and hypoglycemia (coefficient = 0.140, 95%CI: 0.128-0.247, $P = 0.008$). This indirect effect remained significant after adjusting for all confounding factors in both Model 1 ($P = 0.013$) and Model 2 ($P = 0.015$). In contrast, the direct path HGI → Hypoglycemia was non-significant (coefficient = 0.020, 95%CI: 0.157-0.197, $P = 0.828$), suggesting that the association between HGI and hypoglycemia is fully mediated by HbA1c [Figure 3].

Table 1. Baseline characteristics by HGI category

	Low HGI N = 394	Moderate HGI N = 397	High HGI N = 412	P
HGI	-0.13 (0.46)	0.61 (0.17)	1.68 (0.73)	< 0.001
Female sex (%)	215 (54.56)	209 (52.64)	243 (58.98)	0.092
Age (years)	70.38 (8.17)	70.77 (7.68)	70.69 (8.18)	0.772
Weight (kg)	66.61 (11.24)	67.85 (10.83)	66.96 (10.05)	0.246
BMI (kg/m²)	25.21 (3.48)	25.73 (3.36)	25.78 (3.63)	0.030
Duration of T2DM (years)	18.58 (7.12)	17.68 (7.01)	19.68 (7.33)	< 0.001
FBG (mmol/L)	8.30 (2.50)	7.79 (2.07)	8.59 (2.77)	< 0.001
2hPG (mmol/L)	12.74 (4.27)	12.49 (3.91)	14.61 (4.47)	< 0.001
HbA1c (%)	6.56 (0.98)	7.07 (0.91)	8.49 (1.51)	< 0.001
Predicted HbA1c (%)	6.68 (1.08)	6.47 (0.89)	6.81 (1.20)	< 0.001
ALT (mmol/L)	20.48 (10.52)	20.48 (10.52)	22.12 (12.37)	0.082
AST (mmol/L)	19.19 (6.39)	19.96 (6.44)	23.66 (78.99)	0.337
GGT (mmol/L)	25.21 (16.56)	28.45 (21.82)	29.96 (28.57)	0.010
Creatinine (mmol/L)	68.28 (16.58)	68.79 (16.84)	65.67 (15.41)	0.014
Total cholesterol (mmol/L)	4.99 (1.00)	5.05 (1.06)	5.08 (1.11)	0.456
Triglycerides (mmol/L)	1.59 (1.12)	1.75 (1.65)	1.71 (1.20)	0.188
HDL-C (mmol/L)	1.37 (0.35)	1.35 (0.36)	1.30 (0.32)	0.011
LDL-C (mmol/L)	3.02 (0.85)	3.04 (0.86)	3.12 (0.87)	0.225
SBP (mmHg)	132.31 (16.07)	132.62 (17.45)	135.05 (17.67)	0.044
DBP (mmHg)	73.65 (9.57)	74.19 (9.90)	73.20 (10.66)	0.383
Pulse	79.90 (12.57)	77.64 (11.10)	78.06 (10.91)	0.013
Hyperlipemia (%)	123 (30.1)	152 (38.9)	132 (32.4)	0.024
NAFLD (%)	94 (23.0)	106 (27.1)	97 (23.8)	0.358
CHD (%)	75 (18.3)	72 (18.4)	90 (22.1)	0.313
Hypertension (%)	209 (51.1)	199 (50.9)	203 (49.8)	0.918
Diabetes treatment				
Intensive therapy (%)	60 (14.7)	64 (16.4)	116 (28.4)	< 0.001
Diet and exercise (%)	16 (4.06)	26 (6.54)	17 (4.12)	0.142
Oral hypoglycemic drugs (%)	300 (76.14)	298 (75.06)	290 (70.38)	0.258
Sulfonylureas (%)	86 (21.83)	53 (13.35)	47 (11.40)	< 0.001
Metformin (%)	123 (31.22)	112 (28.21)	132 (32.03)	0.515
Acarbose (%)	133 (33.76)	137 (34.50)	122 (29.61)	0.301
Insulin (%)	74 (18.78)	73 (18.39)	139 (33.74)	< 0.001
Family history of T2DM (%)	199 (50.51)	175 (44.08)	183 (44.42)	0.446
Current smoker (%)	83 (21.07)	75 (18.89)	71 (17.23)	0.568
Alcohol use (%)	55 (13.96)	47 (11.84)	30 (7.28)	0.014

HGI: Hemoglobin glycation index; BMI: body mass index; T2DM: type 2 diabetes mellitus; FBG: fasting blood glucose; 2hPG: 2-hour postprandial blood glucose; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; NAFLD: nonalcoholic fatty liver disease; CHD: coronary heart disease.

Table 2. Relationship between HGI and hypoglycemia risk

Model	Event (n, %)	HGI	OR (95%CI)	P	P for trend
Crude		HGI [*]	1.242 (1.083-1.425)	0.002	
	99 (25.13%)	Low HGI	Ref	Ref	0.005
	105 (26.44%)	Moderate HGI	1.072 (0.779-1.474)	0.671	
	140 (33.98%)	High HGI	1.534 (1.130-2.082)	0.006	
Model 1		HGI [*]	1.264 (1.098-1.454)	0.001	
	99 (25.13%)	Low HGI	Ref	Ref	0.004
	105 (26.44%)	Moderate HGI	1.086 (0.786-1.499)	0.618	
	140 (33.98%)	High HGI	1.611 (1.177-2.204)	0.003	
Model 2		HGI [*]	1.255 (1.089-1.446)	0.001	
	99 (25.13%)	Low HGI	Ref	Ref	0.003
	105 (26.44%)	Moderate HGI	1.086 (0.785-1.504)	0.617	
	140 (33.98%)	High HGI	1.603 (1.167-2.201)	0.002	

^{*} HGI as a continuous covariate. Model 1: Adjusted for Age, sex, Hyperlipemia, Hypertension, family history of T2DM, NAFLD, ALT, AST, GGT, TC, LDL-C, DBP, and duration of T2DM; Model 2: Model 1+ Triglycerides, creatinine, DBP, SBP, CHD, Pulse, Tumor history, Smoking, and Alcohol consumption. HGI: Hemoglobin glycation index; OR: odds ratio; CI: confidence interval; T2DM: type 2 diabetes mellitus; NAFLD: non-alcoholic fatty liver disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; DBP: diastolic blood pressure; SBP: systolic blood pressure; CHD: coronary heart disease.

Table 3. Mediation effect of HbA1c on the association between HGI and hypoglycemia

Path	Crude			Model 1			Model 2		
	OR/Coefficient	95%CI	P	OR/Coefficient	95%CI	P	OR/Coefficient	95%CI	P
HGI → HbA1c	1.027	0.960-1.093	< 0.001	1.027	0.960-1.093	< 0.001	1.042	0.977-1.11	< 0.001
HGI → Hypoglycemia	0.020	-0.157-0.197	0.828	0.017	-0.160-0.195	0.847	0.031	-0.153-0.215	0.742
HbA1c → Hypoglycemia	0.125	0.013-0.236	0.020	0.126	0.014-0.238	0.026	0.132	0.014-0.249	0.028
HGI → HbA1c → Hypoglycemia	0.140	0.128-0.247	0.008	0.142	0.130-0.248	0.013	0.157	0.015-0.265	0.015

Model 1: Adjusted for Age, sex, Hyperlipemia, Hypertension, family history of T2DM, NAFLD, ALT, AST, GGT, TC, LDL-C, DBP, and duration of T2DM; Model 2: Model 1+ Triglycerides, creatinine, DBP, SBP, CHD, Pulse, Tumor history, Smoking, and Alcohol consumption. HbA1c: Glycated hemoglobin; HGI: hemoglobin glycation index; OR: odds ratio; CI: confidence interval; T2DM: type 2 diabetes mellitus; NAFLD: non-alcoholic fatty liver disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; DBP: diastolic blood pressure; SBP: systolic blood pressure; CHD: coronary heart disease.

Moderation by BMI in the association between HGI and hypoglycemia

Table 4 shows the moderating effect of BMI on the association between HGI and hypoglycemia. The moderation was significant along the path HGI → HGI × BMI → HbA1c (coefficient = 0.019, 95%CI: 0.004-0.040, $P = 0.022$). The simple slope analysis showed that the HGI-hypoglycemia association remained significant at BMI values of one standard deviation below the mean (effect size = 0.946, 95%CI: 0.855-1.044), the mean (effect size = 1.026, 95%CI: 0.960-1.093), and one standard deviation above the mean (effect size = 1.104, 95%CI: 1.013-1.194). After adjusting for confounding factors, the moderating effect of BMI remained significant in both Model 1 ($P = 0.022$) and Model 2 ($P = 0.021$). Figure 3 illustrates the moderated mediation paths.

Table 4. Moderating effect of BMI on the association between HGI and HbA1c

Mediator		Crude	Model 1			Model 2		
			Effect size/Coefficient	95%CI	P	Effect size/Coefficient	95%CI	P
BMI	Mean - 1 SD	0.946	0.855-1.044	< 0.001	0.950	0.855-1.044	< 0.001	0.969
BMI	Mean	1.026	0.960-1.093	< 0.001	1.027	0.960-1.093	< 0.001	1.042
BMI	Mean + 1 SD	1.104	1.013-1.194	< 0.001	1.104	1.014-1.194	< 0.001	1.116
HGI → HGI * BMI → HbA1c		0.022	0.004-0.040	0.019	0.022	0.004-0.041	0.019	0.021

Model 1: Adjusted for Age, sex, Hyperlipemia, Hypertension, family history of T2DM, NAFLD, ALT, AST, GGT, TC, LDL-C, DBP, and duration of T2DM; Model 2: Model 1+ Triglycerides, creatinine, DBP, SBP, CHD, Pulse, history of Tumor, Smoking, and Alcohol consumption. BMI: Body mass index; HGI: hemoglobin glycation index; HbA1c: glycated hemoglobin; CI: confidence interval; T2DM: type 2 diabetes mellitus; NAFLD: nonalcoholic fatty liver disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; DBP: diastolic blood pressure; SBP: systolic blood pressure; CHD: coronary heart disease.

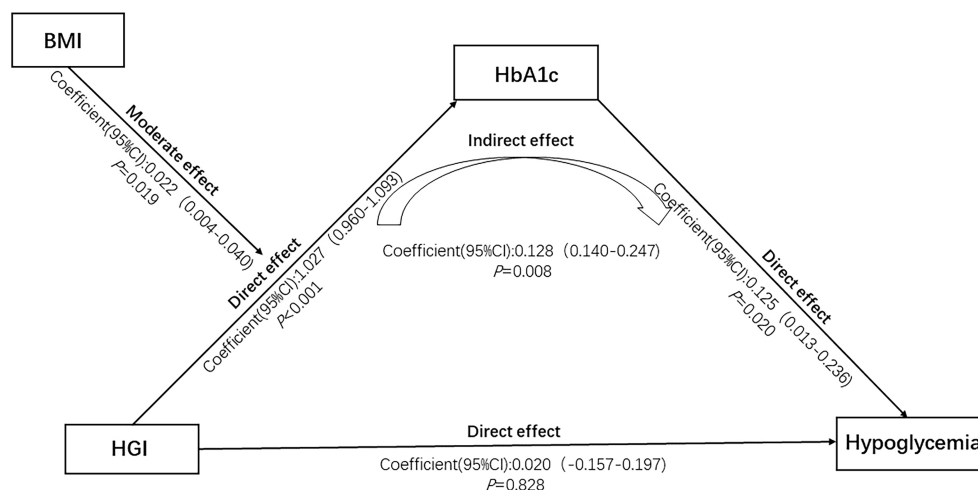


Figure 3. Moderated mediation analysis of the association between HGI and hypoglycemia. HGI: Hemoglobin glycation index; HbA1c: glycated hemoglobin; BMI: body mass index.

DISCUSSION

We explored the association between HGI and hypoglycemia in T2DM patients across eight communities in Beijing and examined the moderating effects of HbA1c and BMI on this association. Our results showed that a higher HGI was significantly associated with an increased risk of hypoglycemia. Moderated mediation analysis confirmed that the link between HGI and hypoglycemia was mediated by HbA1c and moderated by BMI.

HbA1c reflects average blood glucose levels over time but is influenced by individual factors such as erythrocyte turnover, enzyme activity, and intracellular pH^[16,17]. Consequently, individuals with the same mean blood glucose may exhibit different HbA1c levels. To account for these differences, Hempe *et al.* (2002) introduced the HGI, calculated as the difference between observed and predicted HbA1c levels, with predicted HbA1c derived from linear regression of FBG on actual HbA1c^[18]. The HGI has been shown to capture variations in glucose metabolism in pediatric type 1 diabetes patients^[19], and is associated not only

with individual glucose metabolism but also with diabetes complications^[20]. Hypoglycemia is a common complication, particularly in patients with longer disease duration or on intensive hypoglycemic treatment. It disrupts glucose homeostasis and increases the risk of vascular complications. Prior studies have demonstrated that HGI predicts severe hypoglycemia and major adverse cardiovascular events in T2DM patients^[20]. In our cohort, patients with higher HGI more frequently used insulin and sulfonylureas, both of which are known to cause iatrogenic hypoglycemia^[21]. Additional factors affecting severe hypoglycemia include age, diabetes duration, medications, and HbA1c levels^[22], with HbA1c being a key predictor. Notably, a nested case-control study reported a U-shaped relationship between HbA1c and the first hypoglycemia-related hospitalization in adults with T2DM, with risk increasing at both low and high HbA1c levels^[23]. Higher HbA1c levels may indicate impaired glycemic stability and reduced hypoglycemia defenses^[24], whereas lower HbA1c levels can predispose patients on intensive therapy to iatrogenic hypoglycemia^[25,26].

Although both HGI and HbA1c are associated with hypoglycemia, few studies have examined the direct pathway linking HGI to hypoglycemia in T2DM patients. Our mediation analysis suggests HbA1c mediates this relationship. Mechanistically, HGI reflects individual glucose metabolism; changes in HGI influence blood glucose and, in turn, HbA1c levels. In patients with impaired islet function, these changes increase the likelihood of hypoglycemia.

Our moderated mediation analysis further indicated that BMI modulates the relationship between HGI and HbA1c, possibly reflecting alterations in individual metabolism. Higher BMI, often associated with overweight or obesity, may induce glucose tolerance or impair insulin sensitivity^[27,28], thereby influencing the HGI-HbA1c relationship. Overall, our findings suggest that the association between HGI and hypoglycemia risk is influenced by multiple mechanisms, including HbA1c and BMI. This study provides a theoretical basis for understanding the link between HGI and diabetes complications, although more studies are needed to confirm the relationship.

Limitations

Our study has several limitations. First, the sample included only 1,203 T2DM patients from eight Beijing communities, which may introduce selection bias. Second, HGI was calculated via regression of individual FBG on baseline HbA1c, but demographic factors such as race and sex may influence HGI; standardized calculation methods across populations are required. Third, hypoglycemia was self-reported, introducing potential recall bias. Fourth, we did not measure parameters reflecting erythrocyte turnover (e.g., ferritin, erythropoietin, reticulocyte counts), which may confound HGI calculations. Fifth, direct measures of insulin resistance, such as HOMA-IR, were unavailable; as insulin resistance affects glucose homeostasis and glycation, its absence may contribute to residual confounding. Sixth, despite adjustment for several confounders, others such as glucagon levels and the insulin types were not recorded. Finally, clinical implementation of HGI is limited by the need for both HbA1c and fasting glucose measurements, population variability, lack of standardized calculations and cut-offs, and limited interventional evidence. Addressing these gaps is essential to translate HGI from an epidemiological marker to a practical clinical tool.

Conclusion

Clinically, HGI may serve as a useful adjunctive biomarker for stratifying hypoglycemia risk in T2DM patients, particularly when HbA1c alone does not fully capture individual glycemic patterns. Incorporating HGI into routine assessments could identify patients at higher risk of hypoglycemia despite similar mean glucose levels, facilitating personalized therapy. We found that higher HGI is significantly associated with increased hypoglycemia risk. The path from HGI to hypoglycemia is mediated by HbA1c and moderated by

BMI. Interventions targeting HbA1c and BMI may help reduce hypoglycemia risk in T2DM patients.

DECLARATIONS

Authors' contributions

Wrote the manuscript: Liu H

Performed the statistical analyses: Hu X (Xiaodong Hu), Wang A

Collected the data: Kang S

Administered the questionnaires: Hu X (Xiaona Hu)

Assumed full responsibility for data integrity and the accuracy of the analyses: Mu Y

Revised the manuscript: Wang Y, Lyu Z

Designed the study: Wang Y, Lyu Z

All authors approved the final manuscript.

Availability of data and materials

The data and analytical methods are available from the corresponding author upon reasonable request.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee of Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine (Approval No.: 2011-14). All participants provided written informed consent prior to enrolment, in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

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