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ORIGINAL ARTICLE

Retrospective Study

Relationship between hemoglobin glycation index and risk of hypoglycemia in type 2 diabetes with time-in-range in target

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Abstract

BACKGROUND

In patients with type 2 diabetes mellitus (T2DM), the risk of hypoglycemia also occurs in at a time-in-range (TIR) of > 70%. The hemoglobin glycation index (HGI) is considered the best single factor for predicting hypoglycemia, and offers new perspectives for the individualized treatment of patients with well-controlled blood glucose levels that are easily ignored in clinical settings.

AIM

To investigate the relationship between HGI and hypoglycemia and the implications of HGI on hypoglycemia in T2DM with TIR > 70%.

METHODS

All participants underwent a 7-days continuous glucose monitoring (CGM) using a retrospective CGM system. We obtained glycemic variability indices using the CGM system. We defined HGI as laboratory hemoglobin A1c minus the glucose management indicator. Patients were categorized into low HGI (HGI < 0.5) and high HGI groups (HGI ≥ 0.5) according to HGI median (0.5). Logistic regression and receiver operating characteristic curve analyses were used to determine the risk factors for hypoglycemia.

RESULTS

We included 129 subjects with T2DM (54.84 ± 12.56 years, 46% male) in the study. Median TIR score was 90%. The high HGI group exhibited lower TIR and greater time below range with higher hemoglobin A1c than the low HGI group; this suggests more glycemic excursions and an increased incidence of hypoglycemia in the high HGI group. Multivariate analyses revealed that mean blood glucose, standard deviation of blood glucose and HGI were independent risk factors for hypoglycemia. Receiver operating characteristic curve analysis indicated that the HGI was the best predictor of hypoglycemia. In addition, the optimal cut-off points for HGI, mean blood glucose, and standard deviation of blood glucose in predicting hypoglycemia were 0.5%, 7.2 mmol/L and 1.4 mmol/L respectively.

CONCLUSION

High HGI was significantly associated with greater glycemic excursions and increased hypoglycemia in patients with TIR > 70%. Our findings indicate that HGI is a reliable predictor of hypoglycemia in this population.

Key Words: Hemoglobin glycation index; Hypoglycemia; Type 2 diabetes mellitus; Continuous glucose monitoring; Time in range

Core Tip: Our study focused on the relationship between hemoglobin glycation index and hypoglycemia in patients with type 2 diabetes and time-in-range > 70%. Our findings suggest that a high hemoglobin glycation index was significantly associated with greater glycemic excursions and increased hypoglycemia and was the best predictor of the occurrence and severity of hypoglycemia in this population.

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INTRODUCTION

Hemoglobin A1C is widely recognized as the gold standard for evaluating glycemic control and is significantly associated with chronic complications of diabetes mellitus[1]. While hemoglobin A1C can provide an average blood glucose level over the past three months, it fails to accurately evaluate fluctuations in blood glucose levels and hypoglycemia episodes[2,3]. Patients with similar hemoglobin A1C values may experience variations in glucose fluctuations[4]. Therefore, different patients with similar hemoglobin A1C experience different complications. Therefore, a novel index is required to facilitate precise glucose management. With the increasing use of continuous glucose monitoring (CGM) system in recent years, several glucose control parameters other than hemoglobin A1C have been proposed[5]. Among these parameters, time in range (TIR) and glucose management indicator (GMI) are proven novel measures for evaluating glycemic control[6,7].

The TIR is an important metric for evaluating glycemic control and strongly correlates with diabetic complications[8]. Therefore, TIR is more precise than hemoglobin A1C for accessing glycemic control[9]. Patients who achieve TIR within the target range experience less glycemic fluctuation and episodes of hypoglycemia[10]. However, a recent study suggested that some patients who meet TIR target range still experience significant hypoglycemia[11]. Given that patients with diabetes are at a higher risk of mortality due to hypoglycemia, identifying the potential factors contributing to hypoglycemic episodes in patients who achieve targeted TIR is essential.

The GMI can be easily obtained from CGM data; it is a crucial indicator for evaluating glucose status[8]. However, hemoglobin A1C and GMI do not always align[12]. There is a significant disparity between GMI and actual hemoglobin A1C values in some patients, which inhibits the effective utilization of GMI in clinical practice[12]. Therefore, further investigation of this discrepancy between GMI and laboratory hemoglobin A1C levels is important so that clinicians can help their patients effectively manage glycemic control and establish personalized glycemic targets.

To illustrate the discordance between the predicted hemoglobin A1C and laboratory hemoglobin A1C, the hemoglobin glycation index (HGI), calculated as the measured hemoglobin A1C minus GMI, was derived[4]. High HGI value was associated with increased incidence of diabetes-related complications and comorbidities[13,14]. In addition, a high HGI has been proved to attribute to the occurrence of hypoglycemia in patients with poor glucose control[15]. Hence, glycemic hypoglycemia is considered a bridge between high HGI and diabetes-associated complications. However, previous studies investigating the relationship between HGI and hypoglycemia mainly focused on populations whose blood glucose level was beyond the target but not on those with well glycemic control. Patients with good glycemic control may still experience diabetic complications; notable, this population exhibited more episodes of hypoglycemia. Nevertheless, the potential association between HGI and hypoglycemia in this particular population remains elusive. Therefore, invest-

igating the relationship between the HGI and hypoglycemia in patients with TIR > 70% may help clinicians establish effective glycemic control and reduce the incidence of diabetes-associated complications in this population. Therefore, in this study, we explored the role of HGI in assessing glycemic status in patients with type 2 diabetes and a TIR > 70%.

MATERIALS AND METHODS

Study design and population

This single-center retrospective study was conducted at the Department of Endocrinology and Metabolic Diseases, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong Province, China, between June 2017 and December 2019 (Figure 1). The inclusion criteria were as follows: (1) Met the 1999 World Health Organization diagnostic criteria for type 2 diabetes mellitus (T2DM) and age > 18 years; (2) Antihyperglycemic treatment was stable for at least 3 months prior to admission; (3) Laboratory-measured hemoglobin A1c levels were measured and a 7-days CGM was simultaneously applied on the same day simultaneously; and (4) Patients without conditions that may interfere with hemoglobin A1C measurement, such as anemia, hemoglobinopathies, severe renal failure (estimated glomerular filtration rate < 30 mL/minutes/1.73 m^2), and pregnancy. The exclusion criteria included allergies to the CGM sensors and poor compliance with the use of CGM.

Anthropometric indices and laboratory examination

Body mass index was calculated using standard methods [body mass index = weight (kg)/ height^2 (m^2)]. Systolic blood pressure and diastolic blood pressure were measured thrice and averaged. Blood tests were performed after an overnight fast. Laboratory hemoglobin A1C levels were determined using high-performance liquid chromatography with an automated analyzer (Bio-Rad D10; Bio-Rad Laboratories, Hercules, CA, United States) with the whole blood samples. The reference range for laboratory hemoglobin A1C was 4.3%-6.1%, with intra- and inter-batch coefficients of variation of 0.46% and 0.99%, respectively. Hemoglobin, hematocrit, and red blood cell distribution widths in whole blood samples were measured using a fully automated analyzer (Maccura Biotechnology, Chengdu, China). Serum was obtained after centrifugation of whole blood at 3000 rpm for 10 minutes and subsequently analyzed for total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol using a Hitachi Model 7600 Series Automatic Analyzer.

CGM

All subjects underwent a 7-days CGM with a professional retrospective CGM system (iPro™2, Medtronic Minimed Inc., Northridge, CA, United States) following their admission. At least four times of capillary blood glucose monitoring per day were conducted during the CGM period, and capillary blood glucose values were entered into the CGM system monitor for calibration purposes. The CGM data were subsequently downloaded using Carelink iPro and analyzed using GlyCulator 2.0. Only the data sets with adequate glucose data (≥ 70% per day) were included. Data collected on the days of sensor insertion and detachment were considered unstable calibration data and were excluded[16]. Invalid data with evidence of CGM malfunction or sensor loss were excluded from further analysis. Glycemic variability indices adopted in this study included[8]: (1) Mean blood glucose (MBG) is the average BG concentration based on CGM data; (2) Standard deviation of blood glucose (SDBG) is the standard deviation of the total blood glucose within 7 days; (3) Coefficient of variability of glycemia (%CV: SDBG/MBG × 100); (4) The mean amplitude of glycemic excursions (MAGE): The arithmetic mean of the differences between consecutive peaks and nadirs with measurement in the peak-to-nadir direction by the first qualifying excursion; and (5) Absolute means of daily differences (MODD): The mean of absolute differences between glucose values at the same time on two consecutive days. TIR (3.9-10.0 mmol/L), time below range (TBR < 3.9 mmol/L) and time above range (TAR > 10.0 mmol/L) were also obtained from the CGM system. GMI was calculated by CGM-derived mean glucose using the published equation [GMI (%) = 3.31 + 0.02392 × mean glucose in mg/dL][17]. HGI was defined as laboratory hemoglobin A1C minus GMI, and the subjects were divided into two subgroups according to the median HGI (median: 0.5). Patients with HGI < 0.5 were designated as low HGI subgroup while those with HGI ≥ 0.5 were classified as high HGI subgroup.

Definition of hypoglycemia

In accordance with international consensus guidelines, a level 1 hypoglycemic episode was defined as ≥ 15 consecutive minutes of sensor glucose < 3.9 mmol/L, a level 2 hypoglycemic period was defined as sensor glucose < 3.0 mmol/L for ≥ 15 consecutive minutes, both ending at the start of the first 15-minutes period with a sensor glucose ≥ 3.9 mmol/L or 3.0 mmol/L[18,19]. Nocturnal hypoglycemia was defined as hypoglycemia occurring between 10 pm and 6 am[20]. Nocturnal hypoglycemia was further divided into two periods: Hypoglycemia at night (10 pm to 3 am) and early morning (3 am to 6 am).

Statistical analysis

All data analyses were performed using the SPSS software version 26.0 (SPSS IBM Inc., Chicago, IL, United States). Data are represented as mean ± SD for normally distributed variables and as median with interquartile range for non-normally distributed data variables. Continuous variables were compared with analysis using the Student's *t*-test or Mann-Whitney testing, and categorical variables were compared using the χ^2 test or Fisher's exact probabilities. Multiple logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CI) to evaluate the risk factors for

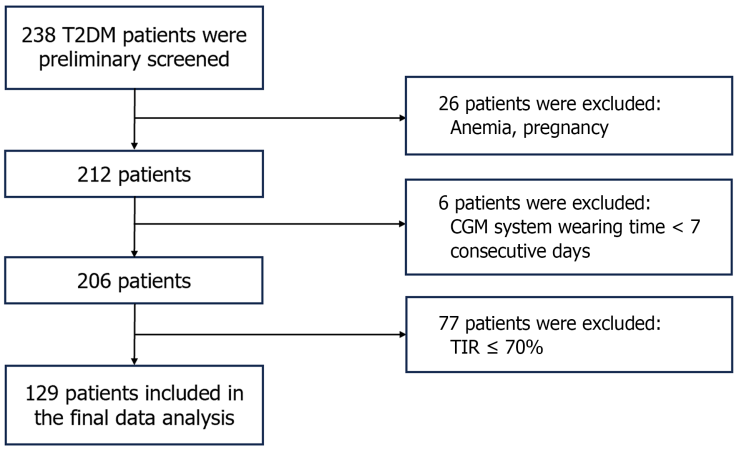

Figure 1 Flow chart of the trial. T2DM: Type 2 diabetes mellitus; CGM: Continuous glucose monitoring; TIR: Time in range.

hypoglycemia. Multivariate logistic regression analysis was used with a forward selection method, and only factors that showed *P* values of < 0.25 on univariate analysis were chosen in the multivariate model after excluding multicollinearity by Spearman's correlation analysis. The validity of CGM-derived metrics for hypoglycemia diagnosis was estimated using receiver operating characteristic (ROC) curves, optimal cutoff values, area under the curve, sensitivity, and specificity with 95%CI. Statistical significance was set at $P < 0.05$.

RESULTS

Clinical characteristics and CGM parameters of subjects

A total of 129 patients with an average age of 54.84 ± 12.56 years and 54 males (41.9%) were enrolled into our study. There were no significant differences in the treatment between the high and low HGI groups, and the proportion of patients receiving sulfonylurea and insulin therapy, who might be potentially more prone to hypoglycemia, was relatively small. Although the rate of insulin use was higher in the high-HGI group than that in the low-HGI group, the difference was not statistically significant (35% *vs* 21%, $P = 0.071$). Additionally, the high-HGI group exhibited decreased hematocrit levels, whereas no variations in red cell distribution width were observed between the two groups. The mean laboratory hemoglobin A1C level in all subjects was 6.63% ± 1.27%. Moreover, laboratory hemoglobin A1C was significantly higher in the high HGI group than that in the low HGI group (7.43% ± 1.30 % *vs* 5.95% ± 0.71%, $P < 0.001$) (Table 1).

There were no significant differences in GMI values between high and low HGI groups (6.11% ± 0.70% *vs* 6.06% ± 0.63%, $P = 0.752$). Glycemic variability indices, including CV (21.41% ± 6.78% *vs* 24.76% ± 8.31%, $P = 0.017$), largest amplitude of glycemic excursions (LAGE) (8.26% ± 2.89% *vs* 9.63 ± 3.06%, $P = 0.005$) and MODD [1.30 (0.50) *vs* 1.50 (0.60), $P = 0.024$] were significantly higher in high HGI group than those in low HGI group, while no significant differences of SDBG, MBG and MAGE were observed between groups. The TIR was significantly lower in the high HGI group than in the low HGI group. An absolute difference in TBR was also observed between the two groups, whereas no statistically significant difference was observed in time above range between the groups (Table 2).

Hypoglycemia status and factors affecting hypoglycemia in type 2 diabetes

Despite higher hemoglobin A1C levels, the high HGI group exhibited a significantly higher incidence of hypoglycemia than the low HGI group (67% *vs* 14%, $P < 0.001$) (Table 1). The time, frequency, and severity of hypoglycemia were further compared between the high- and low-HGI groups. The frequencies of hypoglycemia in the early morning (from 3 am to 6 am) and at night (from 10 pm to 3 am) were significantly lower in the low-HGI group than in the high-HGI group (3.78% *vs* 10.14%, $P < 0.0001$ and 3.67% *vs* 10.96%, $P < 0.0001$, respectively). We next evaluated the duration of the glucose for level 1 hypoglycemia (below 3.9 mmol/L) or level 2 hypoglycemia (below 3.0 mmol/L) and found that the percentage of time for either was significantly higher in the high HGI group than those in the low HGI group (Figure 2). Logistic regression analyses revealed that low MBG, high SDBG, and high HGI were independent risk factors for the presence of hypoglycemia, whereas sex, age, laboratory hemoglobin A1c, hematocrit, LAGE, MAGE, MODD, and use of insulin and/or sulfonylurea treatment did not show a relationship with hypoglycemia in type 2 diabetes patients with TIR > 70% (Table 3).

Predicting factors for hypoglycemia

ROC curve analysis was conducted to evaluate the effects of HGI, MBG, and SDBG on hypoglycemia. The area under the ROC curve for HGI (0.79, 95%CI: 0.71-0.87, $P < 0.0001$) was superior to that for MBG (0.67, 95%CI: 0.58-0.75, $P = 0.0003$) and SDBG (0.67, 95%CI: 0.58-0.75, $P = 0.0004$) in predicting hypoglycemia in type 2 diabetes patients with TIR > 70%. ROC curve analysis showed that the optimal cutoff values of HGI, MBG, and SDBG for predicting hypoglycemia were 0.5%, 7.2 mmol/L and 1.4 mmol/L respectively (Figure 3A). We next conducted ROC curve analysis by combining the three

Table 1 Clinical characteristics of study participants

Characteristic	Total	HGI < 0.5	HGI ≥ 0.5	*P* value
Participants, *n* (%)	129	72 (56)	57 (44)	
Age (years), mean ± SD	54.84 ± 12.56	53.33 ± 12.28	56.75 ± 12.75	0.414
Female	70 (54)	35 (49)	35 (61)	0.148
BMI (kg/m^2)	24.52 ± 3.11	24.33 ± 12.14	24.76 ± 6.62	0.392
Duration of diabetes (months), medians (IQR)	73 (109.5)	73 (85.17)	97.33 (127.77)	0.287
Diabetes therapy, *n* (%)				
Diet only	25 (19)	18 (25)	7 (12)	0.077
Sulfonylurea	21 (16)	11 (15)	10 (18)	0.812
Metformin	58 (45)	27 (38)	31 (54)	0.075
α-glucosidase inhibitor	33 (26)	18 (25)	15 (26)	0.865
DPP4 inhibitor	28 (22)	18 (25)	10 (18)	0.391
SGLT-2 inhibitor	5 (4)	3 (4)	2 (4)	0.848
CSII/MDI	35 (27)	15 (21)	20 (35)	0.071
SBP (mmHg), mean ± SD	127.35 ± 14.09	126.22 ± 13.51	128.77 ± 14.79	0.375
DBP (mmHg), mean ± SD	80.84 ± 9.19	79.79 ± 8.06	82.18 ± 10.37	0.104
TC (mmol/L), mean ± SD	4.39 ± 1.07	4.33 ± 1.02	4.46 ± 1.13	0.790
TG (mmol/L), mean ± SD	1.63 ± 1.26	1.63 ± 1.48	1.64 ± 0.93	0.285
LDL-C (mmol/L), mean ± SD	2.68 ± 0.89	2.60 ± 0.86	2.78 ± 0.92	0.275
HDL-C (mmol/L), mean ± SD	1.13 ± 0.48	1.19 ± 0.58	1.07 ± 0.30	0.216
Laboratory HbA1c (%), mean ± SD	6.63 ± 1.27	5.95 ± 0.71	7.43 ± 1.30	< 0.001[a]
Hemoglobin (g/L), mean ± SD	133.84 ± 14.68	136.33 ± 13.21	131.70 ± 15.92	0.085
Hemotocrit (%), mean ± SD	0.40 ± 0.04	0.41 ± 0.04	0.39 ± 0.05	0.042[a]
Red cell distribution width (%), mean ± SD	0.13 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.556
Hypoglycemia, *n* (%)	49	10 (14)	39 (67)	< 0.001[a]

[a]*P* < 0.05, compared with the values from two groups.

HGI: Hemoglobin glycation index; BMI: Body mass index; DPP4: Dipeptidyl peptidase-4; SGLT-2: Sodium-glucose co-transporter type 2; CSII: Continuous subcutaneous insulin infusion; MDI: Multiple daily injection; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; TG: Triglyceride; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; HbA1c: Hemoglobin A1c; IQR: Interquartile range.

indicators, which suggested the area under the ROC curve for combination of high HGI, low MBG and high SDBG (0.91, 95%CI: 0.84-0.95, *P* < 0.0001) was higher than that for combination of high HGI and low MBG (0.83, 95%CI: 0.75-0.89, *P* < 0.0001) and combination of high HGI and high SDBG (0.82, 95%CI: 0.74-0.88, *P* < 0.0001) (Figure 3B). Based on these cutoff values, patients were divided into four groups according to the number of hypoglycemia predictors, in order to analyze the differences in the severity and occurrence time of hypoglycemia: Group 0 (no risk factors) (HGI < 0.5% and MBG ≥ 7.2 mmol/L and SDBG < 1.4 mmol/L); group 1 (one risk factor) (HGI ≥ 0.5% or MBG < 7.2 mmol/L or SDBG ≥ 1.4 mmol/L); group 2 (two risk factors) (HGI ≥ 0.5% and MBG < 7.2 mmol/L or HGI ≥ 0.5% and SDBG ≥ 1.4 mmol/L or MBG < 7.2 mmol/L and SDBG ≥ 1.4 mmol/L); group 3(three risk factors) (HGI ≥ 0.5% and MBG < 7.2 mmol/L and SDBG ≥ 1.4 mmol/L). The incidence of glucose < 3.9 mmol/L and < 3.0 mmol/L was near 0% for the group with none of the three predictors, 24.1% and 7.4% respectively for the groups with a single predictor, 85.1% and 25.5% respectively for the groups with two predictors, 100% and 73.3% respectively for the groups with three predictors, suggesting a linear relationship across the groups. It is noteworthy that when patients meet the criteria of HGI ≥ 0.5% and MBG < 7.2 mmol/L and SDBG ≥ 1.4 mmol/L, the incidence of glucose < 3.9 mmol/L was 100%, while the incidence of hypoglycemia (glucose < 3.0 mmol/L) is 0% when there were no risk factors. In addition, the incidence of hypoglycemia in the early morning and at night also showed a significant increase as the number of predictors increased. The frequency of hypoglycemia in the early morning and at night was 7.7% and 0%, respectively, in cases with 0 risk factors; 24.1% and 18.5%, respectively, in cases with 1 risk factor; 51.1% and 57.4%, respectively, in cases with 2 risk factors; and 80% and 93.3%, respectively, in cases with 3 risk factors (Figure 4).

Table 2 Continuous glucose monitoring parameters

Characteristic	Total	HGI < 0.5	HGI ≥ 0.5	*P* value
Participants, *n* (%)	129	72 (56)	57 (44)	
GMI (%), mean ± SD	6.09 ± 0.67	6.11 ± 0.70	6.06 ± 0.63	0.752
Average glucose (mmol/L), mean ± SD	7.11 ± 1.06	7.13 ± 1.10	7.08 ± 1.02	0.885
SDBG (mmol/L), mean ± SD	1.67 ± 0.64	1.59 ± 0.63	1.77 ± 0.64	0.961
CV (%), mean ± SD	22.89 ± 7.65	21.41 ± 6.78	24.76 ± 8.31	0.017[a]
MAGE (mmol/L), mean ± SD	4.08 ± 1.81	3.88 ± 1.72	4.35 ± 1.91	0.742
LAGE (mmol/L), mean ± SD	8.86 ± 3.03	8.26 ± 2.89	9.63 ± 3.06	0.005[a]
MODD (mmol/L), medians (IQR)	1.40 (0.70)	1.30 (0.50)	1.50 (0.60)	0.024[a]
TIR (% of time 39-10 mmol/L), medians (IQR)	90 (17)	93.50 (13)	86 (16)	0.002[a]
TBR (% of time < 3.9 mmol/L), medians (IQR)	1 (5)	0 (2)	2 (11)	< 0.001[a]
TAR (% of time > 10 mmol/L), medians (IQR)	6 (13)	4.50 (11)	8 (12)	0.068

[a]*P* < 0.05, compared with the values from two groups.

HGI: Hemoglobin glycation index; GMI: Glucose management indicator; SDBG: Standard deviation blood glucose; CV: Coefficient of variation; MAGE: Mean amplitude of glucose excursion; LAGE: Largest amplitude of glycemic excursions; MODD: Mean of daily differences; TIR: Time in range; TBR: Time below range; TAR: Time above range.

Table 3 Clinical markers of glycemia variables for hypoglycemia analyzed by univariate and multiple logistic regression analyses

	Univariate logistic regression			Multiple logistic regression		
	χ^2	*P* value	OR (95%CI)	Wald χ^2	*P* value	OR (95%CI)
Sex (female/male)	0.82	0.37	0.73 (0.36-1.45)			
Age	4.25	0.04[a]	0.42 (0.19-0.96)			
BMI	0.09	0.77	1.11 (0.55-2.25)			
Laboratory HbA1c	0.36	0.55	0.81 (0.41-1.62)			
Hemotocrit	1.81	0.18	1.75 (0.78-3.95)			
MBG	4.26	0.04[a]	0.45 (0.21-0.96)	9.05	< 0.01[a]	0.17 (0.05-0.54)
SDBG	9.74	< 0.01[a]	3.44 (1.58-7.47)	5.30	0.02[a]	5.37 (1.28-22.46)
LAGE	3.41	0.07	7.56 (0.88-64.67)			
MAGE	6.95	0.01[a]	2.62 (1.28-5.35)			
MODD	0.32	0.57	1.36 (0.46-4.01)			
HGI	6.98	< 0.01[a]	2.65 (1.29-5.44)	4.65	0.03[a]	2.46 (1.09-5.58)
Use of insulin and/or sulfonylurea	0.30	0.58	1.22 (0.60-2.51)			

[a]*P* < 0.05.

OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; HbA1c: Hemoglobin A1c; MBG: Mean blood glucose; SDBG: Standard deviation blood glucose; LAGE: LAGE: Largest amplitude of glycemic excursions; MAGE: Mean amplitude of glucose excursion; MODD: Mean of daily differences; HGI: Hemoglobin glycation index.

DISCUSSION

In this observational study, we investigated the relationship between HGI and hypoglycemia in patients with type 2 diabetes and TIR > 70%. Our findings indicate that the high HGI group demonstrated more hypoglycemia episodes and more instances of glucose fluctuations than the low HGI group, even in patients with type 2 diabetes with a TIR > 70%. Our study also found that the best single predictor of hypoglycemia was HGI, and hypoglycemia should be of note when

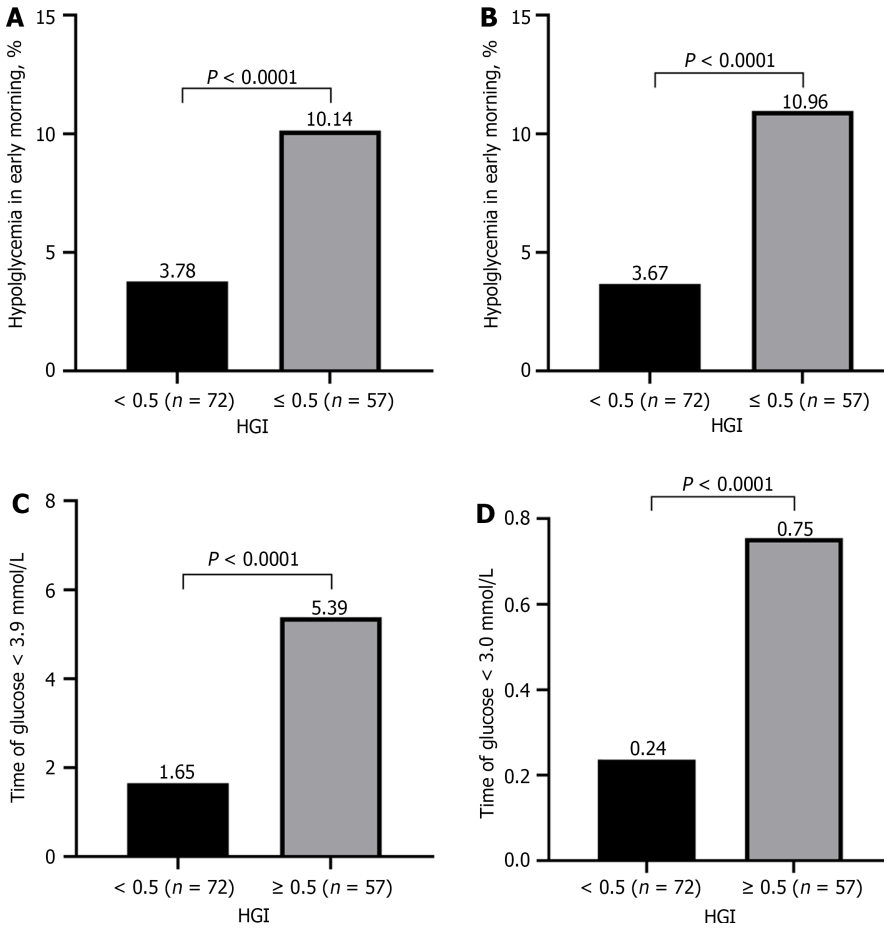

Figure 2 The differences in hypoglycemia between high hemoglobin glycation index and low hemoglobin glycation index groups. A and B: Frequency of hypoglycemia in early morning (A) and nighttime (B); C and D: Frequency of time of glucose < 3.9 mmol/L (C) and < 3.0 mmol/L (D). HGI: Hemoglobin glycation index.

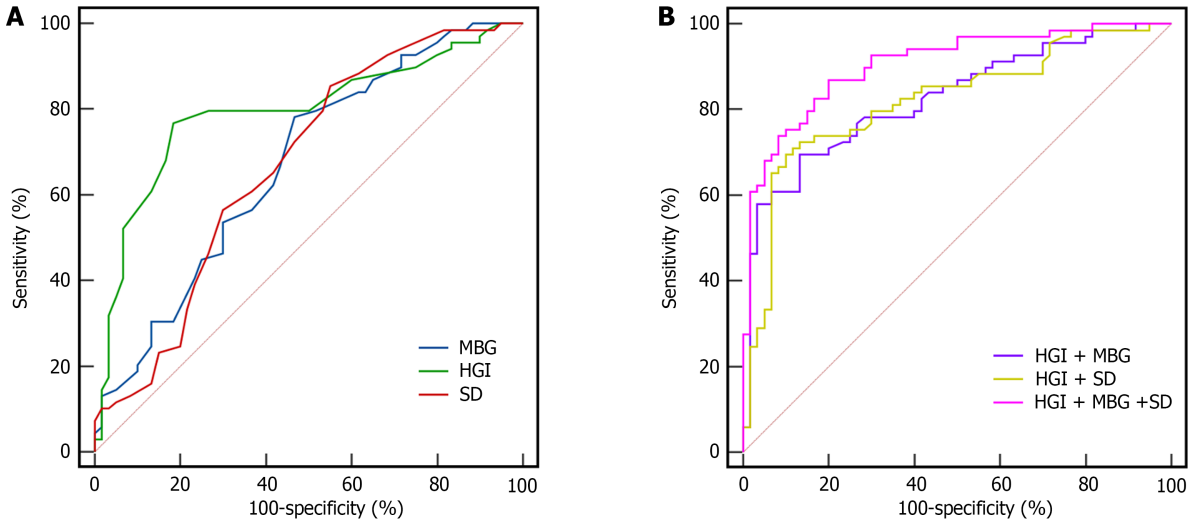

Figure 3 Receiver operator characteristic curve. A: Receiver operator characteristic curve of high hemoglobin glycation index, low mean blood glucose and high standard deviation blood glucose in assessing risk of hypoglycemia among people with type 2 diabetes mellitus; B: Receiver operator characteristic curve of combination of high hemoglobin glycation index, low mean blood glucose and high standard deviation blood glucose in assessing risk of hypoglycemia among people with type 2 diabetes mellitus. HGI: Hemoglobin glycation index; MBG: Mean blood glucose; SD: Standard deviation.

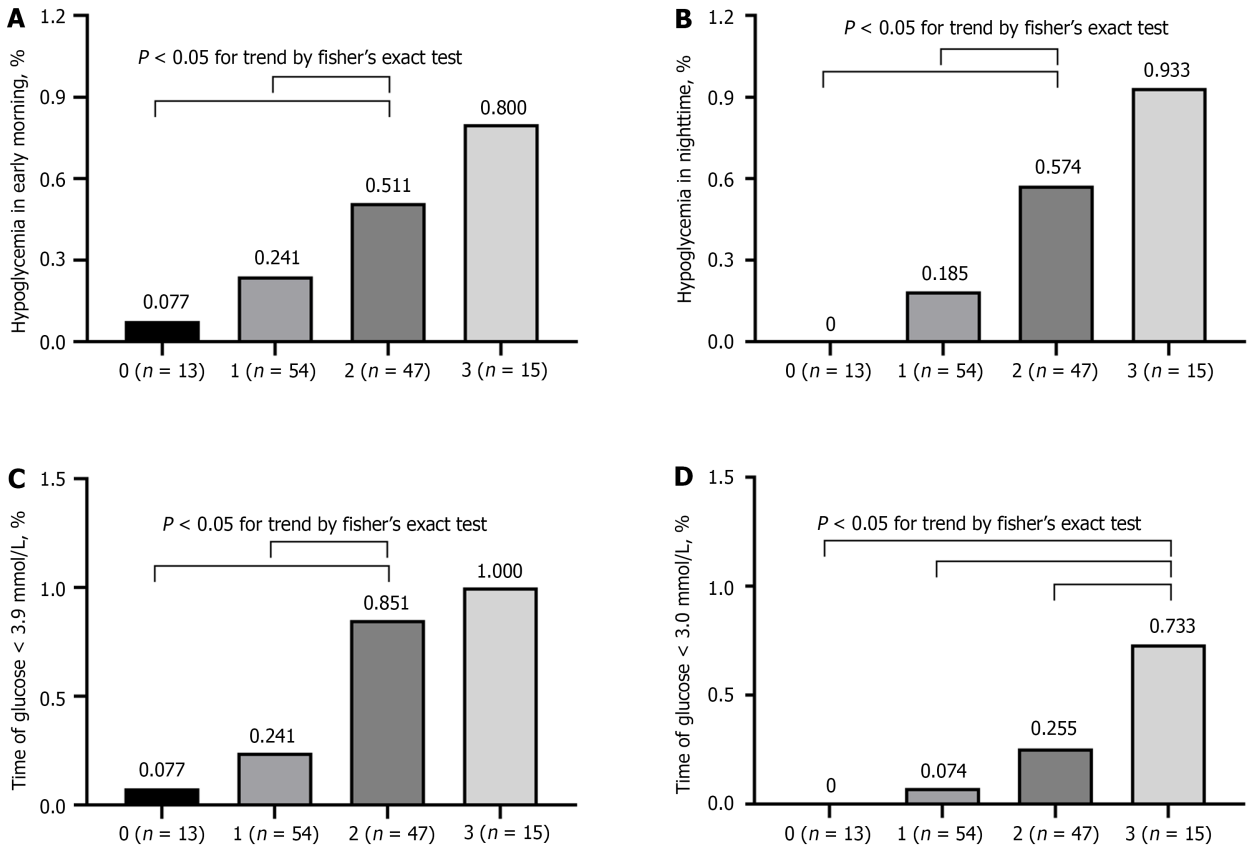

Figure 4 Relationship between the number of risk factors and hypoglycemia. A and B: Frequency of hypoglycemia in early morning (A) and nighttime (B); C and D: Frequency of time of glucose < 3.9 mmol/L (C) and < 3.0 mmol/L (D). Number of risk factors for hypoglycemia: 0 [hemoglobin glycation index (HGI) < 0.5% and mean blood glucose (MBG) ≥ 7.2 mmol/L and standard deviation blood glucose (SDBG) < 1.4 mmol/L]; 1 (HGI ≥ 0.5% or MBG < 7.2 mmol/L or SDBG ≥ 1.4 mmol/L); 2 (HGI ≥ 0.5% and MBG < 7.2 mmol/L or HGI ≥ 0.5% and SDBG ≥ 1.4 mmol/L or MBG < 7.2 mmol/L and SDBG ≥ 1.4 mmol/L); 3 (HGI ≥ 0.5% and MBG < 7.2 mmol/L and SDBG ≥ 1.4 mmol/L).

the laboratory hemoglobin A1C was greater than GMI by ≥ 0.5% in this population. Moreover, hypoglycemia was more likely to occur in patients with higher HGI (HGI ≥ 0.5%), lower MBG level (MBG < 7.2 mmol/L) and larger fluctuations in BG level (SDBG ≥ 1.4 mmol/L), suggesting that the combined assessment of these three variables was useful in detecting hypoglycemia in this population.

Recently, the HGI has emerged as a novel parameter to demonstrate the discordance between predicted hemoglobin A1C and laboratory hemoglobin A1C. Patients with high HGI experience higher incidence of diabetes-associated complications. Patients in the Diabetes Control and Complications Trial study were stratified into low-, moderate-, and high-HGI groups. After seven years of follow-up, patients in the high-HGI group had a significantly higher risk of developing retinopathy and nephropathy than those in the other groups[21]. Ahn *et al*[22] investigated the relationship between the HGI and cardiovascular diseases in patients with prediabetes and individuals with treatment-naïve diabetes and found that patients in the highest HGI tertile had a significantly increased risk of composite cardiovascular diseases. However, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial suggested that the HGI may serve as a predictor of macrovascular and microvascular diseases, but not better than hemoglobin A1C, in patients with diabetes receiving intensive treatment[14]. Another ancillary study to Action to Control Cardiovascular Risk in Diabetes trial was conducted to investigate whether intensive hypoglycemic therapy (hemoglobin A1C goal < 6.0%) can reduce cardiovascular events in T2DM with high cardiovascular risk compared with standard treatment (hemoglobin A1C goal 7.0%-7.9%). However, the study was terminated after 3.7 years due to an increase in all-cause mortality among patients in the intensive treatment group. Interestingly, *post-hoc* subgroup analysis revealed that higher mortality in intensively treated patients with T2DM was observed only in the high HGI subgroup[23]. Patients who received intensive treatment in the ADVANCE and Action to Control Cardiovascular Risk in Diabetes trials experienced increased hypoglycemia. As a result, the discrepancy in the association between high HGI and diabetic complications in previous studies might be partly attributed to increased hypoglycemia during intensive treatment. However, research on the HGI has mainly focused on the relationship between the HGI and chronic complications and comorbidities in diabetes, whereas little attention has been paid to the relationship between the HGI and hypoglycemia in well-controlled patients.

As mentioned earlier, hemoglobin A1C may not precisely reflect blood glucose levels, even in well-controlled patients, which could lead to potential errors in clinical evaluation and treatment[24-26]. For patients with a high HGI and TIR in the target region, the actual glycosylated hemoglobin levels were higher than the predicted hemoglobin A1C. Thus, intensive hypoglycemic treatment may be administered in this population if glycosylated hemoglobin levels are used as

treatment targets. In contrast, for patients with low HGI and TIR in the target who were considered to have fewer chronic complications of diabetes, relaxation of the criteria for the control target may be considered. However, patients with strict glycemic control are prone to hypoglycemia. Hypoglycemia causes cognitive impairment and myocardial ischemia, which can result in sudden death[27]. Therefore, the relationship between the HGI and hypoglycemia needs to be clarified in patients with diabetes and good glycemic control. Interestingly, our study indicated that although with higher hemoglobin A1C and TIR in target, hypoglycemia occurred more frequently in the high HGI group than in the low HGI group.

In this study, we found no statistically significant difference in GMI values between the high and low HGI groups, but the high HGI group showed a significant increase in hemoglobin A1C, which points to the likelihood of greater blood glucose fluctuations in the high HGI group. Consistent with this, our results showed that the high HGI group had higher levels of CV, LAGE, and MODD, suggesting more glucose excursions. Additionally, higher hemoglobin A1C was more likely to lead to intensified hypoglycemic treatment by clinical physicians, which may be the reason for the higher incidence of hypoglycemia in the high HGI group. Moreover, we found that the frequency of nocturnal hypoglycemia and the severity of overall hypoglycemia were much higher in the high HGI group than in the low HGI group. These results suggest that the risk of hypoglycemia also occurred in patients with type 2 diabetes with TIR in target; thus, neither hemoglobin A1C nor GMI were proper predictors of hypoglycemia in this population. Our study showed that the HGI can serve as an effective indicator to compensate for the limitations of hemoglobin A1C in assessing glycemic control.

TIR has emerged as a significant metric in clinical studies of diabetes. Several investigations have demonstrated that TIR is closely associated with the risk of complications and mortality in patients with diabetes[28,29]. Consequently, clinical guidelines have incorporated TIR as a key objective for blood glucose management, recommending a target of > 70% for most non-pregnant adult patients with diabetes[8]. In our study, the median TIR of patients was 90%, leading to the assumption that patients had good glycemic control, potentially overlooking the occurrence of hypoglycemia. However, the single use of TIR has been criticized for not being adequately sensitive to hypoglycemia[30,31], and it has been reported that 7% of diabetic individuals with TIR greater than 70% were hospitalized for hypoglycemia or diabetic ketoacidosis[11]. Consequently, it is imperative to incorporate additional indicators to enhance the clinical glycemic management of patients with a TIR exceeding 70%. Our findings support and extend those of previous studies on glycemic control in well-controlled diabetes management. We found that HGI can be used as an indicator for assessing blood glucose to improve clinical outcomes, especially in patients with diabetes whose TIR is greater than 70%, which may be easily ignored in clinical settings.

In the present study, MBG, SDBG, and HGI were identified as risk factors for hypoglycemia, and HGI was suggested as the most effective individual measurement for predicting hypoglycemia. Previous studies have demonstrated that the occurrence of hypoglycemia increases with strict glycemic control[32]. Consistently, we found that patients with TIR > 70% were more likely to develop hypoglycemia with a higher HGI. Moreover, our study suggests that the HGI is the best predictor of the occurrence and severity of hypoglycemia. We further combined the indexes of HGI, MBG and SDBG, whose cutoff values were 0.5%, 7.2 mmol/L and 1.4 mmol/L respectively, with a sensitivity of 87% and a specificity of 80%. The results showed that patients with hemoglobin A1C higher than GMI by ≥ 0.5%, MBG < 7.2 mmol/L, and SDBG ≥ 1.4 mmol/L had a significantly higher risk for clinically hypoglycemia, no matter in early morning or nighttime. Previous studies have shown that using hemoglobin A1C alone as the glycemic control target might lead to irrational clinical use of hypoglycemic agents and setting unreasonable and unattainable blood glucose goals for patients to maintain good glycemic control[33-36]. Therefore, combinations of the HGI and other CGM indices, such as the HGI and hemoglobin A1C, provide individualized treatment for patients.

Our study had several strengths. First, we specifically targeted patients with a TIR exceeding 70%, a demographic that is frequently neglected regarding glycemic variability and the associated risk of hypoglycemia in clinical settings. Furthermore, our results indicate that the HGI may provide significant advantages for glucose management in patients with diabetes. Importantly, the integration of the HGI, MBG, and SDBG further improved the predictive sensitivity for hypoglycemia, thereby aiding clinicians in personalized glycemic management strategies for patients with a TIR greater than 70%. Our findings may help identify patients at a potentially greater risk of hypoglycemia and guide appropriate therapeutic schedules for patients with strict glycemic control.

Limitation

The limitations of our study include its retrospective design and the relatively small sample size. In addition, 7 days wearing time of the CGM device was considered shorter than 10-14 days in previous studies. However, minimal differences were observed between the 14- and 7-day GMI[37], suggesting that the variance around the estimation error for the CGM metrics is similar[17]. Further prospective studies with larger sample sizes and longer wearing time of iPro2 are warranted.

CONCLUSION

In this retrospective study, we found that a higher HGI was significantly associated with increased hypoglycemia, even in patients with TIR in target. The HGI was found to be the best predictor of hypoglycemia. Patients with a TIR exceeding 70% who exhibited lower MBG, greater glycemic excursions, and higher HGI were more likely to develop hypoglycemia.

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