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Impacts of glycemic variability on the relationship between glucose management indicator from iPro™2 and laboratory hemoglobin A1c in adult patients with type 1 diabetes mellitus

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Abstract

Aims: Our aim was to investigate the impact of glycemic variability (GV) on the relationship between glucose management indicator (GMI) and laboratory glycated hemoglobin A1c (HbA1c).

Methods: Adult patients with type 1 diabetes mellitus (T1D) were enrolled from five hospitals in China. All subjects wore the iPro™2 system for 14 days before HbA1c was measured at baseline, 3 months and 6 months. Data derived from iPro™2 sensor was used to calculate GMI and GV parameters [standard deviation (SD), glucose coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE)]. Differences between GMI and laboratory HbA1c were assessed by the absolute value of the hemoglobin glycation index (HGI).

Results: A total of 91 sensor data and corresponding laboratory HbA1c, as well as demographic and clinical characteristics were analyzed. GMI and HbA1c were $7.20 \pm 0.67\%$ and $7.52 \pm 0.73\%$, respectively. The percentage of subjects with absolute HGI 0 to lower than 0.1% was 21%. GMI was significantly associated with laboratory HbA1c after basic adjustment (standardized $\beta = 0.83$, $p < 0.001$). Further adjustment for SD or MAGE reduced the standardized β for laboratory HbA1c from 0.83 to 0.71 and 0.73, respectively (both $p < 0.001$). In contrast, the β remained relatively constant when further adjusting for CV. Spearman correlation analysis showed that GMI and laboratory HbA1c were correlated for each quartile of SD and MAGE (all $p < 0.05$), with the corresponding correlation coefficients decreased across ascending quartiles.

Conclusions: This study validated the GMI formula using the iPro™2 sensor in adult patients with T1D. GV influenced the relationship between GMI and laboratory HbA1c.

Keywords: glucose management indicator, glycated hemoglobin A1c, glycemic variability, diabetes mellitus, type 1

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Introduction

Laboratory glycated hemoglobin A1c (HbA1c) is a standard metric for the assessment of glycemic control in patients with diabetes mellitus. However, there are several limitations in the use of laboratory HbA1c for assessing glycemic control. Laboratory HbA1c could not assess hypoglycemia or glycemic variability (GV) and is easily affected by certain conditions such as renal failure, hemoglobinopathy and chronic liver disease.[1]

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Thus, estimating glycemic control by laboratory HbA1c alone may not reveal a thorough characterization of glycemic exposure for some patients, especially those with large blood glucose fluctuations in the short term and those with frequent exposure to hypoglycemia such as patients with type 1 diabetes mellitus (T1D).[2]

Continuous glucose monitoring (CGM) has become a useful tool for assessing blood glucose levels in the last few years. It can provide more detailed and comprehensive blood glucose information *via* numerous data. The glucose metrics derived from CGM data partially compensate for the limitations of laboratory HbA1c.[3,4] Recently, 15 of these metrics have been recommended as key metrics by international guidelines and consensuses.[5–7] The glucose monitoring index (GMI), derived from CGM mean glucose and previously named as estimated A1C, is one of them.[5,8]

The GMI formula was conceived using data derived from specific types of CGM sensors including Dexcom G4 and G5 (Dexcom, Inc., San Diego, CA), and mainly based on Caucasian populations.[8] It was well known that the accuracy of measurement varied among different types of sensors. Although GMI formula has been validated by using Guardian Sensor 3 (Medtronic Inc., CA) and Freestyle Navigator II (Abbott Diabetes Care, CA) glucose sensors,[9] the validation of the GMI formula for the retrospective CGM system with SOF sensor (Medtronic Minimed Inc., Northridge, CA, USA) in Asian populations is still lacking.

Moreover, previous studies have reported the discordance between GMI and laboratory HbA1c.[8–12] Therefore, the assessment of glycemic control based on laboratory HbA1c or GMI alone might mislead clinical decisions. The exact reasons for such a discrepancy remain unclear. Several studies have evaluated the effect of glycemic variability (GV) on the relationship between mean glucose and laboratory HbA1c, but the results were inconsistent. Most of these studies used self-monitoring of blood glucose (SMBG) data to calculate GV and mean glucose, and the results showed that GV had no or minimal effect on the relationship between mean glucose and laboratory HbA1c.[13–15] On the contrary, a study by Kuenen JC *et al.* used CGM data instead of SMBG data and found that GV influenced the association between mean glucose and laboratory HbA1c in patients with T1D, with high GV leading to a higher HbA1c level for the same mean glucose.[16] Given that the GMI was calculated from CGM derived mean glucose, we speculated that GV assessed by CGM data may have an impact on the relationship between GMI and laboratory HbA1c.

Therefore, the aim of this study was to validate the GMI formula using the iPro™2 system with SOF sensor in Chinese adult patients with T1D and to further explore the impacts of GV on the relationship between GMI and laboratory HbA1c.

Methods

Study design and participants

All data analyzed in the current study was extracted from an ongoing study registered on www.clinicaltrials.gov (identifier: NCT03522870). This multicenter and randomized study was designed to evaluate the effect of a novel flash glucose monitoring system and conventional SMBG in adult patients with T1D who have inadequate glycemic control. The protocol of study design was summarized herein.

Briefly, patients with T1D aged 18 years and older were recruited. Other main inclusion criteria were duration of diabetes $\geqslant$ 1 year, HbA1c 7–10%, treated with continuous subcutaneous insulin infusion or multiple daily injections at a stable regimen, and SMBG at least three times per day for at least 3 months prior to study entry. Key exclusion criteria included having used CGM 3 months prior to study entry, severe chronic diabetic complications or critical illness, being pregnant or planning pregnancy, or any condition that could affect impact reliability of the HbA1c measurement (hemoglobinopathy, hemolytic anemia, or chronic liver disease).

After a 2-week screening, eligible patients were randomly assigned to an intervention group of flash glucose monitoring (FGM) system (Freestyle Libre®; Abbott Diabetes Care, Witney, Oxon, UK) or control group of conventional SMBG (Bayer®; Bayer Consumer Care AG). All patients received general diabetes management education including dietary, exercise, SMBG, and insulin titration algorithms at enrollment, with reinforcement at 3- and 6-month visits. This trial was

reviewed by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University [Ethics Approval Number: (2017) 2-5] and conformed to the Declaration of Helsinki. All patients gave written informed consent before the screening.

Data collection

The 14 consecutive days of subcutaneous interstitial glucose data for all subjects was obtained *via* the professional retrospective CGM (iPro™2, Medtronic Minimed Inc., Northridge, CA, USA) at baseline, 3 months and 6 months. During the 14 days, SMBG was performed at least four times per day using the Bayer® blood glucose meter (Bayer®; Bayer Consumer Care AG). The SMBG data were downloaded from the respective meters and were used to calibrate CGM data. Records which contained at least 80% of glucose data during the wearing time (presented as the percentage of data collected per week) were included in the analysis.

Laboratory HbA1c was measured centrally at baseline, 3 months and 6 months by an automated analyzer (Bio-Rad D10; Bio-Rad Laboratories, Hercules, CA) using the high-performance liquid chromatography technique, with a reference range of 4.3–6.1% and intra-batch and inter-batch coefficients of variation of 0.46% and 0.99%, respectively.

Demographic and clinical characteristics including age, sex, duration of diabetes, body mass index (BMI), treatment method, and blood routine were collected at each visit by trained physicians.

For the purpose of the current analysis, CGM data and corresponding HbA1c, as well as demographic and clinical characteristics, at 3 months and 6 months were included.

CGM parameter

CGM data from iPro™2 sensor was downloaded *via* Carelink iPro and was calculated using Glyculator 2.0 software, which was allowed for calculation of every index of CGM recommended by the International Consensus.[5,17]

GMI was calculated by applying CGM-derived mean glucose to the equation [GMI (%) = 3.31 + 0.02392 × mean glucose in mg/dl].[8] Hemoglobin glycation index (HGI) was calculated by subtracting the GMI from laboratory HbA1c [HGI = laboratory HbA1c (%) − GMI (%)].[18] Absolute value of HGI was used to describe the discrepancies between the GMI and laboratory-measured HbA1c. HGI groups were determined by HGI value tertile (low HGI, <0.07; moderate HGI, 0.07–0.45; high HGI, >0.45), and the differences of GMI and laboratory HbA1c were compared among different HGI groups.

GV was assessed by the standard deviation (SD), glucose coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE). CV was calculated by dividing the SD by the mean of the corresponding glucose readings. MAGE algorithm was adapted from the P. Baguhrst version.[19] SD and MAGE were stratified according to their quartiles.

Statistical analysis

Data were expressed as means ± SD with approximately normal distributions and medians [interquartile range (IQR)] with non-normal variables or as numbers and percentages for categorical variables. GMI and laboratory HbA1c among different HGI groups were compared by one-way ANOVA with a Bonferroni correction. Univariate linear regression analysis was used to fit the association between GMI and laboratory HbA1c. Multivariable linear regression analysis was performed to examine the relationship between GMI as dependent variable and laboratory HbA1c after adjusting for potential clinical factors including age, sex, duration of diabetes, BMI, treatment method, wearing time, interview time, intervention method, and hemoglobin (Model 1, basic adjustment). Additional adjustment for GV parameters based on Model 1 was also performed. Spearman correlation analysis was used to analyze the correlation between GMI and HbA1c within the quartile categories of SD and MAGE. All statistical analyses were performed using the SPSS version 23.0 software (SPSS Inc., Chicago, IL, USA). A probability level <0.05 was considered significant.

Results

Population characteristics

A total of 91 iPro™2 data and corresponding laboratory HbA1c were included in the analysis,

Table 1. Characteristics of study participants.

Characteristic	*n* = 91
Age (years)	30.45 (24.22, 37.80)
Sex (female/male)	62/29
Duration of diabetes (years)	8.97 (4.87, 13.21)
BMI (kg/m^2)	21.48 ± 1.76
Treatment (CSII/MDI)	30/61
Intervention (FGM/SMBG)	47/44
Interview time (3 months/6 months)	51/40
Laboratory HbA1c (%)	7.52 ± 0.73
GMI (%)	7.20 ± 0.67
Percentage of sensor data/week (%)	91.55 (84.38, 94.60)
SD (mg/dl)	65.61 ± 14.82
CV (%)	41.25 ± 7.65
MAGE (mg/dl)	162.18 ± 34.90
Hematocrit	0.40 ± 0.04
Hemoglobin(g/l)	136.02 ± 11.87
RBC (× 10^{12}/l)	4.69 ± 0.62
WBC (× 10^9/l)	6.09 ± 1.76

Data are mean ± SD or medians (interquartile range).
BMI, body mass index; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variance; FGM, flash glucose monitoring; GMI, glucose management indicator; HbA1c, hemoglobin A1c; MAGE, mean amplitude of glycemic excursions; MDI, multiple daily injections; RBC, erythrocyte count; SD, standard deviation; SMBG, self-monitor of blood glucose; WBC, leukocyte count.

with 51 collected at 3 months (Male/Female, 16/35; FGM/SMBG, 26/25) and 40 collected at 6 months (Male/Female, 13/27; FGM/SMBG, 21/19). Participants had a median (IQR) age of 30.45 (24.22, 37.80) years, with a diabetes duration of 8.97 (4.87, 13.21) years. The mean GMI and laboratory HbA1c were 7.20 ± 0.67% and 7.52 ± 0.73%, respectively. The percentage of the available wearing time of iPro™2 sensor was 91.55 (84.38, 94.60)%. The mean SD, CV, and MAGE were 65.61 ± 14.82 mg/dl, 41.25 ± 7.65% and 162.18 ± 34.90 mg/dl, respectively (Table 1).

Discrepancies between GMI and laboratory HbA1c

Table 2 shows the discrepancies between GMI and laboratory HbA1c among different sensors. The percentage of individuals with similar GMI and laboratory HbA1c (absolute HGI 0 to lower 0.1%) was comparable among the four sensor groups, with a median value ranged from 19% to 21%. The confidence intervals were similar to those using Guardian 3 sensors and Navigator II sensors, but wider than those using Dexcom sensors. The percentage of those with 0.7% and higher deviations of HGI was significantly higher in the iPro™2 group than those with the other three sensors with different confidence intervals.

The discrepancy of GMI and laboratory HbA1c was further compared among different HGI groups. Laboratory HbA1c levels were different across the three HGI groups (low *versus* moderate *versus* high HGI groups, 7.18 ± 0.54% *versus* 7.65 ± 0.61% *versus* 8.24 ± 0.56%, respectively, $p < 0.001$), with the highest laboratory HbA1c in the high-HGI group, while GMI remained similar among the three groups (low *versus* moderate *versus* high HGI group, 7.25 ± 0.53% *versus* 7.13 ± 0.57% *versus* 7.06 ± 0.48%, respectively, $p > 0.05$; Figure 1).

Relationship between GMI and laboratory HbA1c

The univariate linear analysis revealed a significant linear relationship between GMI and laboratory HbA1c ($R = 0.79$, $R^2 = 0.63$, $p < 0.001$; Figure 2). In the multivariable linear regression model (Table 3), the linear relationship between GMI and laboratory HbA1c ($R = 0.83$, $R^2 = 0.68$, $p < 0.001$) persisted significantly after adjusting for age, sex, duration of diabetes, BMI, treatment method, wearing time, interview time, intervention method, and hemoglobin (Model 1). Further adjustment for SD or MAGE (Model 2 and 4) plus Model 1 decreased the standardized β regression coefficients from 0.83 to 0.71 and 0.73, respectively (both $p < 0.001$). In contrast, the β for laboratory HbA1c remained relatively constant when further adjusting for CV (Model 3). Spearman correlation analysis showed that GMI and laboratory HbA1c were correlated in each quartile of SD and MAGE (all $p < 0.05$), with the corresponding correlation coefficients decreased across ascending quartiles (Table 4).

Table 2. Discrepancies between GMI and laboratory HbA1c among different sensors.

Absolute value of HGI (%)	Percentage of values (95% CI)			
	iPro™2 sensor (*n* = 91)	Guardian3 sensor* (*n* = 85)	Navigator II sensor* (*n* = 114)	Dexcom sensors** (*n* = 528)
0 to <0.1	21 (12–29)	19 (11–29)	20 (13–29)	19 (16–22)
⩾0.1	79 (71–88)	81 (71–89)	80 (72–87)	81 (78–84)
⩾0.2	63 (53–73)	66 (55–76)	68 (58–76)	67 (63–71)
⩾0.3	53 (42–63)	54 (43–66)	56 (46–65)	51 (47–55)
⩾0.4	41 (30–51)	42 (32–54)	46 (36–56)	39 (34–43)
⩾0.5	34 (24–44)	32 (22–43)	36 (27–46)	28 (24–32)
⩾0.6	26 (17–36)	24 (15–34)	28 (20–37)	19 (15–22)
⩾0.7	21 (12–29)	13 (7–22)	21 (14–30)	12 (9–15)
⩾0.8	18 (10–26)	11 (5–19)	12 (6–19)	8 (5–10)
⩾0.9	12 (5–19)	5 (1–12)	8 (4–15)	4 (3–6)
⩾1.0	10 (4–16)	3 (1–10)	5 (2–10)	3 (2–4)

CI, confidence interval; GMI, glucose management indicator; HbA1c, hemoglobin A1c; HGI, hemoglobin glycation index.
*Guardian 3 and Navigator 2 data from Leelarathna *et al.*;[9]
**Dexcom data from Bergenstal *et al.*[8]

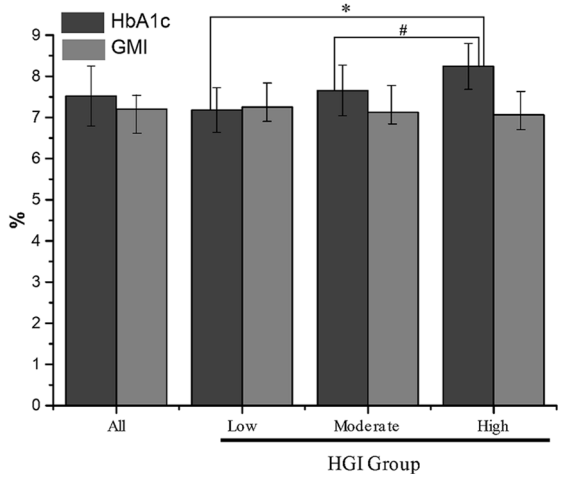

Figure 1. Disagreement between GMI and laboratory HbA1c.
Mean glucose management indicator (GMI) and mean hemoglobin A1c (HbA1c) were compared in all data and separately by hemoglobin glycation index (HGI) group. Data are group means ± SD. GMI was similar to HbA1c in the low-HGI group, lower than HbA1c in the moderate-HGI and the high-HGI group. Dividing the data into HGI groups automatically produces subsets with similar GMI levels but different HbA1c levels (*Low *versus* High, $p = 0.001$; #Moderate *versus* High, $p = 0.001$).

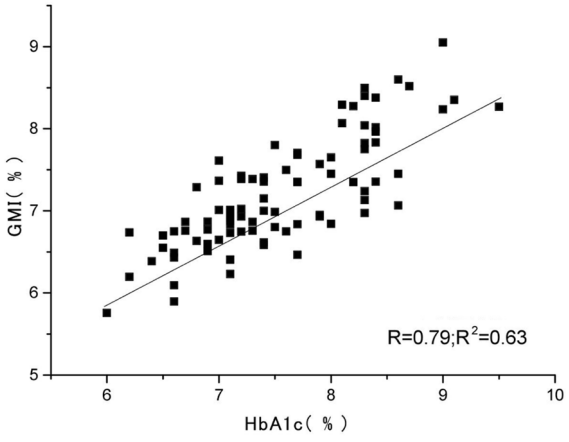

Figure 2. The relationship between GMI and laboratory HbA1c. GMI was measured by continuous glucose monitoring for 14 days before the HbA1c measurement. The solid line is the best fit. The SEM of the slope and the intercept are 0.06 and 0.44, respectively.
GMI, glucose management indicator; HbA1c, hemoglobin A1c; SEM, standard error of the mean.

Table 3. Linear regression analyses for the association between GMI and laboratory HbA1c in adult patients with type 1 diabetes mellitus.

Model	Parameters	R	R^2	Adjusted R^2	B (95% CI)	Standardize β	*p* Value
1	HbA1c	0.83	0.68	0.63	0.75 (0.62–0.88)	0.83	0.000
2	HbA1c	0.85	0.72	0.67	0.65 (0.51–0.78)	0.71	0.000
	SD				0.01 (0.00–0.02)	0.26	0.002
3	HbA1c	0.83	0.69	0.63	0.74 (0.62–0.87)	0.82	0.000
	CV				−0.01 (−0.02–0.01)	−0.09	0.224
4	HbA1c	0.84	0.71	0.66	0.66 (0.53–0.80)	0.73	0.000
	MAGE				0.00 (0.00–0.01)	0.22	0.005

BMI, body mass index; CI, confidence interval; CV, coefficient of variance; GMI, glucose management indicator; HbA1c, hemoglobin A1c; MAGE, mean amplitude of glycemic excursions; SD, standard deviation.
Model 1 was adjusted for age, sex, duration of diabetes, BMI, treatment method, wearing time, interview time, intervention method, and hemoglobin; Model 2 includes all variables in Model 1 plus SD; Model 3 includes all variables in Model 1 plus CV; Model 4 includes all variables in Model 1 plus MAGE.

Table 4. Spearman correlation analysis between GMI and laboratory HbA1c based on quartiles of MAGE and SD.

	R (95% CI)	*p* value
MAGE		
Q1 (*n* = 24)	0.80 (0.60–0.94)	<0.001
Q2 (*n* = 23)	0.78 (0.53–0.93)	<0.001
Q3 (*n* = 22)	0.71 (0.47–0.87)	<0.001
Q4 (*n* = 22)	0.61 (0.28–0.83)	0.003
SD		
Q1 (*n* = 23)	0.78 (0.58–0.92)	<0.001
Q2 (*n* = 23)	0.74 (0.50–0.81)	<0.001
Q3 (*n* = 22)	0.72 (0.42–0.79)	<0.001
Q4 (*n* = 22)	0.56 (0.14–0.73)	0.005

CI, confidence interval; GMI, glucose management indicator; HbA1c, hemoglobin A1c; MAGE, mean amplitude of glycemic excursions; SD, standard deviation.

Discussion

CGM indicators such as GMI and GV, as an adjunct to laboratory HbA1c, are beneficial for clinicians and individuals with diabetes to make personalized management decisions.[8,20] In this study, we observed a discrepancy between GMI (based on iPro™2 system with SOF sensor) and laboratory HbA1c in Chinese adult patients with T1D, especially in those with moderate or high HGI. Moreover, we validated the GMI formula using the iPro™2 system with SOF sensor in this population and found that the linear relationship between GMI and laboratory HbA1c was influenced by GV, as assessed by SD and MAGE.

The percentage of patients with absolute HGI 0 to <0.1% was 21% in this study, which was comparable with that reported in previous studies using the other three sensors (ranging from 19% to 20%),[8,9] while the percentage of patients with 0.7% and higher deviation was higher in this study than those using the other three glucose sensors. There are several possible reasons. First, the wearing time of the sensor was different across the studies [a median of 66 days in Dexcom sensor,[8] 3 months in Guardian 3 and Navigator II,[9] and a median of 13 days (91.55% data/per week) in our study]. However, we consider the wearing time of the sensor comparable among the four studies because it has been confirmed that 14 days of CGM data was able to provide a good estimation of glucose metrics for a 3-month period,[21,22] Second, instrumental bias might also contribute to deviation. Although all four sensors have been approved by the US Food and Drug Administration, it should be borne in mind that the accuracy, sensor life time, and calibration requirement can be varied.[23] Third, the study population included in these studies was different. The participants in our study were Chinese

adult patients with T1D, whereas the cohort used to derive the regression formula for GMI comprised both patients with T1D and type 2 diabetes mellitus.[8]

Moreover, we found significant discrepancies between the GMI and laboratory HbA1c, with the highest laboratory HbA1c in the high-HGI group, while GMI remained similar among the three groups, suggesting that the discrepancies were independent of GMI levels. This result is consistent with those reported by Hempe *et al.* who attributed this discrepancy to the individual differences in laboratory HbA1c and suggested using HGI to quantify it.[18] Notably, a few studies reported that there was an association between HGI and diabetic complications in patients with diabetes, with high HGI values having higher incidences of cardiovascular disease, diabetic retinopathy, and nephropathy.[24–28] These findings as well as our results suggested that HGI should be addressed when assessing glycemic control in patients with T1D.

Furthermore, our study explored the effect of GV on the relationship between GMI and laboratory HbA1c. To our knowledge, the present study was the first study to explore the impact of GV on the relationship between GMI and laboratory HbA1c by using CGM data. First, we validated the linear fitting GMI formula using the iPro™2 sensor in Chinese adult patients with T1D, which also confirmed the linear relationship between GMI and laboratory HbA1c. Second, in the multivariable linear regression analysis, we found the relationship between GMI and laboratory HbA1c remained significant after adjusting for age, sex, duration of diabetes, BMI, treatment method, wearing time, interview time, intervention method, and hemoglobin (basic adjustment). However, further adjustment for SD or MAGE, but not CV, attenuated the association between GMI and laboratory HbA1c. This indicates that the relationship between GMI and laboratory HbA1c is partly mediated by GV as assessed with SD and MAGE. Third, we found that the correlation coefficients between GMI and laboratory HbA1c decreased with the quartiles of SD and MAGE ascending. Based on the previously mentioned findings, we proposed that GV should be taken into consideration when applying GMI or HbA1c for the personalized management of diabetes. For example, patients with stable glucose can choose either GMI or laboratory HbA1c for individual management, while those with large glucose fluctuations would need a combination of GMI and laboratory HbA1c to help us set individual goals.

Our study has some limitations. In our study, GMI was calculated based on a median of 13 days CGM data in our study, which was shorter than those in previous studies, though 10–14 days CGM data was considered sufficient to estimate the CGM metrics for a 3-month period. In addition, the patients enrolled in this study were Chinese adult patients with T1D and our results may not be applicable to patients from other ethnic groups. Finally, similar to other sensors, iPro™2 has a limited range of reliable measurements between 2.2 mmol/L and 22.2 mmol/L and has a lag time in glucose values compared with the venous measured values. Therefore, CGM data could be less precise in patients with high glycemic variability, which might result in underestimation of the influence of GV on the GMI.

In conclusion, we found discrepancies between GMI and laboratory HbA1c in patients with T1D, especially in those with moderate or high HGI. We provided validation of the GMI formula using the iPro™2 sensor in Chinese adult patients with T1D and confirmed that the relationship between GMI and laboratory HbA1c was influenced by GV. Thus, when applying the GMI in the management of patients with T1D, the impacts of HGI and GV should be considered.

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Author contribution(s)

Hongxia Liu: Data curation; Formal analysis; Investigation; Methodology; Project administration; Visualization; Writing-original draft; Writing-review & editing.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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