

Impact of flash glucose monitoring on glycemic control varies with the age and residual β -cell function of patients with type 1 diabetes mellitus

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ABSTRACT

Aims/Introduction: We aimed to explore the clinical factors associated with glycemic variability (GV) assessed with flash glucose monitoring (FGM), and investigate the impact of FGM on glycemic control among Chinese type 1 diabetes mellitus patients in a real-life clinical setting.

Materials and Methods: A total of 171 patients were included. GV was assessed from FGM data. A total of 110 patients wore FGM continuously for 6 months (longitudinal cohort). Hemoglobin A1c (HbA1c), fasting and 2-h postprandial C-peptide, and glucose profiles were collected. Changes in HbA1c and glycemic parameters were assessed during a 6-month FGM period.

Results: Individuals with high residual C-peptide (HRCP; 2-h postprandial C-peptide >200 pmol/L) had less GV than patients with low residual C-peptide (2-h postprandial C-peptide \leq 200 pmol/L; $P < 0.001$). In the longitudinal cohort ($n = 110$), HbA1c and mean glucose decreased, time in range (TIR) increased during the follow-up period ($P < 0.05$). The 110 patients were further divided into age and residual C-peptide subgroups: (i) HbA1c and mean glucose were reduced significantly only in the subgroup aged ≤ 14 years during the follow-up period, whereas time below range also increased in this subgroup at 3 months ($P = 0.047$); and (ii) HbA1c improved in the HRCP subgroup at 3 and 6 months ($P < 0.05$). The mean glucose decreased and TIR improved significantly in the low residual C-peptide subgroup; however, TIR was still lower and time below range was higher than those of the HRCP subgroup at all time points ($P < 0.05$).

Conclusions: HRCP was associated with less GV. FGM wearing significantly reduced HbA1c, especially in pediatric patients and those with HRCP. Additionally, the mean glucose and TIR were also found to improve.

INTRODUCTION

Glucose monitoring is of great importance in diabetes management, and maintaining euglycemia is the main goal of glycemic control. The glycemic evaluation comprises three aspects: (i) chronic hyperglycemia; (ii) hypoglycemia; and (iii) glycemic variability (GV)¹. GV covers two predominant categories: (i) long-term GV, usually characterized by serial hemoglobin A1c

(HbA1c), fasting or postprandial plasma glucose measurements; and (ii) short-term GV, determined by inter-day and between-day GV². Long-term dysglycemia and GV are strong contributors to the development of diabetes complications^{3–5}. Furthermore, long-term GV is associated with mortality in patients with type 1 diabetes⁶, and is also related to cognitive impairment⁷ and depression⁸. To some extent, short-term GV is of increasing concern to clinicians due to the potential risk of precipitating excessive hypoglycemia episodes⁹.

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HbA1c is the gold standard for evaluating long-term glycaemic control; however, it might be misleading to use HbA1c alone¹⁰, and the pursuit of HbA1c targeting can be accompanied by an increase in the frequency of hypoglycemia^{11,12}. As self-monitoring blood glucose is gradually replaced by continuous glucose monitoring (CGM)¹³, a role of CGM in improving glycaemic control and reducing the occurrence of hypoglycemia has emerged^{14–17}. Flash glucose monitors are factory-calibrated and work by intermittently scanning the glucose level in the interstitial fluid every 15 min. Two randomized controlled trials of the FreeStyle Libre[®] (Abbott, Whitney, UK) system in type 1 diabetes patients with well-controlled HbA1c have shown significant reductions in time in hypoglycemia without showing a significant change in HbA1c levels^{18,19}.

Although the benefits of flash glucose monitoring (FGM) on glycaemic control have been explored in many studies^{20–22}, there are limited data showing the real-world clinical experience on sustained use of FGM among type 1 diabetes patients in mainland China. As noted previously, young children with type 1 diabetes are more susceptible to GV and hypoglycemia, cognitive and verbal immaturity presents an additional challenge to identification of hypoglycemia in young children²³. There is a large proportion of young patients with poor pancreatic islet function at our clinic. Previous studies have pointed out that the decline in C-peptide (C-P) in patients with type 1 diabetes is related to the age of onset²⁴, and that islet function is deemed to be associated with hypoglycemia²⁵.

Therefore, in the present study, we aimed to: (i) explore clinical factors associated with GV assessed by FGM; (ii) examine the impact of FGM on glycaemic control in Chinese type 1 diabetes patients; and (iii) further investigate the impact of FGM on patients of different ages and with different levels of residual C-P.

MATERIALS AND METHODS

Participants

This was a retrospective cohort real-life study based on data retrieved from type 1 diabetes patients who chose to purchase Freestyle Libre[®] to help with their glucose management, and were regularly followed up every 3 months in our clinic of the Second Xiangya Hospital, Central South University, Changsha, China, between September 2018 and October 2020. A total of 171 patients were included in the cross-sectional analysis with the following criteria: (i) diagnosis of type 1 diabetes according to the 1999 World Health Organization criteria; (ii) insulin dependency after type 1 diabetes diagnosis; (iii) duration of diabetes > 6 months; and (iv) use of FGM (Freestyle Libre[®]) to help with their glucose management at their own expense. Patients were excluded for one of the following reasons: (i) incomplete glucose data (<75% data captured during FGM); (ii) use of other types of CGM simultaneously; (iii) pregnancy or preparing for pregnancy; or (iv) a comorbid autoimmune disease, such as hyperthyroidism. The study protocol was approved by the Ethics Review Committee of the Second Xiangya Hospital of Central South University (approval number:

2019-198; date granted: 12 November 2019), and it was carried out in accordance with the Declaration of Helsinki. Signed informed consent was obtained from each participant. A total of 110 out of 171 patients continuously used FGM up to 6 months, and their 6-month FGM data and relevant HbA1c values were included in the longitudinal analysis.

Demographics and clinical measurements

Age, sex, diabetes duration, height, weight, body mass index, insulin schema, daily insulin dosage (U/kg/day), HbA1c, fasting blood glucose (FBG), 2-h postprandial blood glucose, fasting C-P (FCP), 2-h C-P (2hCP) after a mixed-meal tolerance test (MMTT) and glucose profiles derived from FGM for all 171 participants were reviewed and extracted from electronic medical records. A standard MMTT (44.4% carbohydrates, 47.7% fat and 7.9% protein) was carried out after 8–10 h of fasting. Patients maintained their long-acting insulin the night before the test and omitted their normal morning insulin. Patients on a pump continued to have a background basal rate but did not take the morning bolus.

HbA1c was measured by automated high-performance liquid chromatography (VARIANT II Hemoglobin Testing System; Bio-Rad Laboratories, Hercules, CA, USA). Serum FCP levels were detected with a chemiluminescent method using an Adivia Centaur XP immunoassay system (Siemens, Munich, Germany). Participants were grouped by their 2hCP after a MMTT as low residual C-P (LRCP; 2hCP \leq 200 pmol/L) or high residual C-P (HRCP; 2hCP >200 pmol/L) based on previously reported distribution of residual C-P production in type 1 diabetes²⁶.

Outcome measures

A total of 110 patients wore an FGM device continuously for up to 6 months and were included in the retrospective longitudinal analysis. The primary outcomes were changes in HbA1c. Secondary outcomes included mean glucose, time in range (TIR; 3.9–10.0 mmol/L), time below range (TBR; <3.9 mmol/L), time above range (>10 mmol/L) at 3 and 6 months. Furthermore, changes in HbA1c or glucose profiles were further investigated by subgroup analysis according to: (i) baseline HbA1c \leq 7.5% versus >7.5%; (ii) \leq 14 years versus >14 years; and (iii) low residual C-P versus high residual C-P.

Statistical analysis

The primary outcome was the change in the mean HbA1c level from baseline at 6 months. A sample size of 86 patients in total determined by G.Power 3.1.9.6 software (Franz Faul; University of Kiel, Kiel, Germany) was planned to have a statistical power of 95% to detect a difference in the mean HbA1c level, as summing a population difference of 0.5%, a correlation between baseline and 6-month values of 0.50, an alpha level of 0.05 and an effect size of 0.25. Finally, we included 110 eligible type 1 diabetes patients to provide sufficient statistical power.

Normally distributed measurement data are presented as the mean \pm standard deviation, and skewed data after normality

Table 1 | Characteristics of all participants and in the low and high residual C-peptide groups

	Total patients (<i>n</i> = 171)	LRCP group (<i>n</i> = 112)	HRCP group (<i>n</i> = 59)	<i>P</i> -value
Sex (male/female)	73/98	48/64	25/34	0.86
Age (years)	12.0 (8.0–24.5)	12.0 (7.5–26.5)	13.0 (8.0–19.0)	0.90
Diabetes duration (years)	1.6 (0.7–3.3)	2.0 (1.1–3.8)	0.7 (0.3–1.6)	<0.001
BMI (kg/m ²)	18.6 ± 3.4	18.7 ± 3.3	18.5 ± 3.6	0.64
Insulin schema (MDI/CSII)	122/49	80/32	42/17	0.55
Insulin dose (U/kg/day)	0.58 ± 0.27	0.62 ± 0.27	0.47 ± 0.24	0.003
HbA1c (%)	7.2 ± 1.0	7.2 ± 0.9	7.0 ± 1.3	0.41
FCP (pmol/L)	29.1 (16.5–128.6)	17.5 (16.5–41.5)	164.5 (134.8–208.3)	<0.001
2hCP (pmol/L)	48.1 (16.5–269.2)	16.7 (16.6–65.2)	402.8 (305.8–594.6)	<0.001
FBG (mmol/L)	7.6 (5.7–9.9)	8.8 (6.0–11.3)	6.8 (5.5–7.6)	<0.001
2hBG (mmol/L)	13.7 (8.5–20.0)	13.0 (6.7–19.7)	15.1 (10.0–20.1)	0.13
TC (mmol/L)	4.2 ± 0.8	4.3 ± 0.8	4.0 ± 0.8	0.07
TG (mmol/L)	0.7 ± 0.3	0.7 ± 0.4	0.7 ± 0.2	0.84
HDL-c (mmol/L)	1.6 ± 0.3	1.6 ± 0.3	1.5 ± 0.4	0.03
LDL-c (mmol/L)	2.2 ± 0.6	2.3 ± 0.6	2.1 ± 0.6	0.24
FGM-derived metrics				
Scan rates (times/day)	14 (10–15)	14 (11–15)	14 (8–21)	0.85
eHbA1c (%)	6.6 ± 1.0	6.8 ± 1.0	6.2 ± 0.9	<0.001
%TAR (>10.0 mmol/L)	23.0 (11.0–35.0)	27.5 (18.0–37.0)	11.0 (4.0–23.0)	<0.001
%TIR (3.9–10 mmol/L)	65.5 ± 15.1	61.4 ± 13.7	75.5 ± 14.9	<0.001
%TBR (<3.9 mmol/L)	8.0 (4.0–13.5)	8.0 (4.0–13.5)	7.0 (3.0–12.0)	0.11
Mean glucose (mmol/L)	7.9 ± 1.6	8.3 ± 1.6	7.2 ± 1.5	<0.001
SD (mmol/L)	3.2 ± 0.9	3.4 ± 0.8	2.5 ± 0.9	<0.001
MAGE (mmol/L)	6.9 ± 2.0	7.5 ± 1.9	5.7 ± 1.8	<0.001
CV (%)	39.5 ± 7.2	41.3 ± 6.1	35.1 ± 7.9	<0.001
LBGI	1.9 (1.1–3.2)	2.0 (1.1–3.2)	1.6 (0.9–2.6)	0.13

Data are shown as the mean ± standard deviation, median (interquartile range) and frequency. *P*-values for the low residual C-peptide (LRCP) group versus the high residual C-peptide (HRCP) group. 2hBG, 2-h postprandial blood glucose; 2hCP, 2-h postprandial C-peptide; BMI, body mass index; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; eHbA1c, estimating A1c, a measure converting the mean glucose from CGM into an estimate of a simultaneously measured laboratory A1c; FBG, fasting blood glucose, FCP, fasting C-peptide, HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; HRCP, high residual C-peptide (2-h postprandial C-peptide >200 pmol/L); LBGI, low blood glucose index; LDL-c, low-density lipoprotein cholesterol; LRCP, low residual C-peptide (2-h postprandial C-peptide ≤ 200 pmol/L); MAGE, mean amplitude of glucose excursions; MDI, multiple daily insulin injection; SD, standard deviation of glucose; TAR, time above range; TBR, time below range; TC, total cholesterol; TG, triglyceride; TIR, time in range.

testing (Shapiro–Wilk test) are presented as the median and interquartile range (IQR). An independent sample *t*-test or the Mann–Whitney *U*-test were used to compare differences between groups. The changes in HbA1c and FGM-derived indices (normally distributed) were calculated by the general linear model. The changes in skewed data were calculated by the Wilcoxon signed-rank test. Spearman's rank correlation was used for the correlation analysis. A two-tailed test was carried out, and *P* < 0.05 was considered statistically significant. SPSS 24.0 software (IBM Corporation, Armonk, NY, USA) was used for statistical analysis.

RESULTS

Characteristics of participants

Of the 171 participants enrolled in the analysis, 57.3% were female. The mean age was 12.0 years (IQR 8.0–24.5) years. The average duration of diabetes was 1.6 (IQR 0.7–3.3) years. The

mean body mass index level was 18.6 ± 3.4 kg/m². The 171 patients were divided into the following two groups according to MMTT-stimulated C-P levels: LRCP group (2hCP ≤ 200 pmol/L, *n* = 112) and HRCP group (2hCP >200 pmol/L, *n* = 59). Details are shown in Table 1.

Relationship between β-cell function and glycemic control

The HRCP group had a significantly shorter duration of diabetes than the LRCP group (0.7 vs 2.0 years, *P* < 0.001), and the required daily insulin dosage of the HRCP group was much smaller (0.47 vs 0.62 U/kg/day, *P* = 0.003). FBG levels were also lower in the HRCP group (6.8 vs 8.8 mmol/L, *P* < 0.001). Regarding glycemic profiles, TIR was much higher in the HRCP group (75.5% vs 61.4%, *P* < 0.001). Time above range, eHbA1c, mean glucose, standard deviation of glucose, mean amplitude of glucose excursions and CV were all lower (*P* < 0.001).

Table 2 | Correlation between glycemc parameters and clinical factors

	All participants (n = 171)				
	TIR	Mean glucose	SD	MAGE	CV
Age (years)	0.010	-0.100	-0.121	-0.101	-0.076
BMI (kg/m ²)	0.050	-0.105	-0.120	-0.136	-0.020
Duration of diabetes (years)	-0.179*	0.052	0.202*	0.181*	0.281**
Daily insulin dosage (U/kg/day)	-0.177*	0.176*	0.225*	0.194*	0.140
HbA1c (%)	-0.626**	0.656**	0.586**	0.555**	0.227*
FBG (mmol/L)	-0.253**	0.335**	0.283**	0.296**	0.046
2hBG (mmol/L)	0.015	0.045	0.005	0.021	-0.052
FCP (pmol/L)	0.359**	-0.218*	-0.418**	-0.393**	-0.435**
2hCP (pmol/L)	0.367**	-0.285**	-0.448**	-0.407**	-0.413**

Values represent Spearman's correlation coefficients. * $P < 0.05$, ** $P < 0.01$. 2hBG, 2-h postprandial blood glucose; 2hCP, 2-h postprandial C-peptide; BMI, body mass index; CV, coefficient of variation; FBG, fasting blood glucose, FCP, fasting C-peptide, HbA1c, hemoglobin A1c; MAGE, mean amplitude of glucose excursions; SD, standard deviation of glucose; TIR, time in range.

Table 3 | Multivariate analysis of clinical factors associated with glycemc parameters

	All participants (n = 171)				
	TIR ($R^2 = 0.398$)	Mean glucose ($R^2 = 0.439$)	SD ($R^2 = 0.377$)	MAGE ($R^2 = 0.355$)	CV ($R^2 = 0.194$)
Age (years)		-0.196**	-0.168*	-0.162*	
Use of CSII	0.046*	-0.186**		-0.155*	
HbA1c (%)	-0.483**	0.489**	0.447**	0.386**	0.165*
FCP (pmol/L)	0.321**				-0.391**
2hCP (pmol/L)		-0.637**	-0.363**	-0.363**	

Multiple stepwise regression analysis was performed with time in range (TIR), mean glucose, standard deviation of glucose (SD), mean amplitude of glucose excursions (MAGE) and coefficient of variation (CV) as the dependent variables, and age, duration of diabetes, body mass index, systolic blood pressure, diastolic blood pressure, daily insulin dosage, hemoglobin A1c (HbA1c), fasting blood glucose, 2-h postprandial blood glucose, fasting C-peptide (FCP), 2-h postprandial C-peptide (2hCP), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, thyroid-stimulating hormone, free triiodothyronine, free thyroxine and use of continuous subcutaneous insulin infusion (CSII) as the independent variables. * $P < 0.05$, ** $P < 0.01$.

Spearman's correlation and multivariate analysis

TIR was correlated with the duration of diabetes, daily insulin dosage, HbA1c, FBG, FCP and 2hCP. Mean glucose, standard deviation of glucose and mean amplitude of glucose excursions were positively associated with daily insulin dosage, HbA1c and FBG, and were inversely correlated with FCP and 2hCP. CV was positively and inversely correlated with duration of diabetes, HbA1c, FCP and 2hCP, respectively (Table 2).

Multivariate analysis was used to assess the effects of different clinical variables on glycemc parameters (Table 3). TIR was correlated with the use of continuous subcutaneous insulin infusion and 2hCP, and inversely associated with HbA1c ($R^2 = 0.398$). Mean glucose was correlated with HbA1c, whereas it was inversely associated with age, use of continuous subcutaneous insulin infusion and 2hCP ($R^2 = 0.439$). Standard deviation of glucose was positively and inversely correlated with HbA1c, age, 2hCP, respectively ($R^2 = 0.377$). Mean amplitude of glucose excursions was correlated with HbA1c, whereas it was inversely associated with age, use of continuous

subcutaneous insulin infusion and 2hCP ($R^2 = 0.355$). In addition, CV was positively and inversely correlated with HbA1c and FCP, respectively ($R^2 = 0.194$).

Retrospective longitudinal cohort analysis

The mean HbA1c of 110 patients decreased at 3 months (7.3% vs 7.9%, $P = 0.022$), and further to 7.1% at 6 months ($P = 0.012$). The HbA1c level in patients with a baseline HbA1c $>7.5\%$ decreased from 9.0% to 7.4% at 3 months ($P < 0.001$), and remained stable at 6 months, whereas no change was noted in those with a baseline HbA1c $\leq 7.5\%$. For glycemc parameters, marked downward trends of mean glucose were found at 3 months (8.1 vs 8.5 mmol/L, $P = 0.024$) and 6 months (7.9 vs 8.5 mmol/L, $P = 0.008$). TIR improved at 3 months (64.9% vs 61.5%, $P = 0.009$) and 6 months (65.8% vs 61.3%, $P = 0.004$). Furthermore, time above range also decreased from 29.4% to 25.8% at 3 months ($P = 0.007$), and further to 24.3% at 6 months ($P = 0.003$). No significant changes of TBR were observed during the follow-up period.

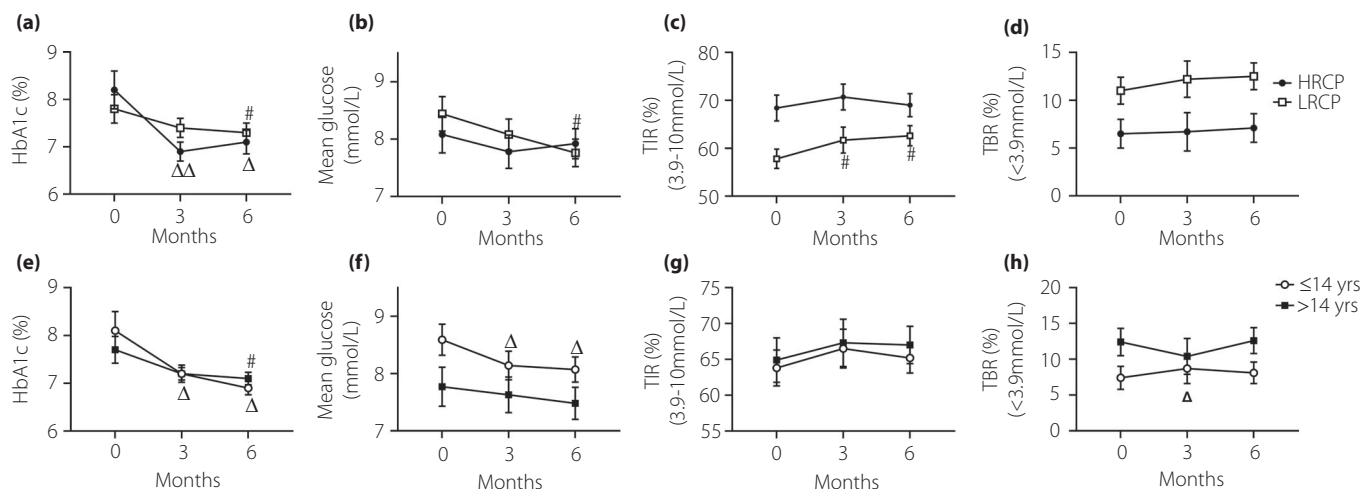


Figure 1 | Changes of hemoglobin A1c (HbA1c) and glycemic parameters in age and residual β -cell function subgroups. Data are expressed with the mean (standard error). Black circles: high residual C-peptide subgroup ($n = 40$); white squares: low residual C-peptide subgroup ($n = 70$); white circles: subgroup aged ≤ 14 years ($n = 69$); black squares: subgroup aged > 14 years ($n = 41$). (a,e) HbA1c, (b,f) mean glucose, time in range (TIR; c, g) and time below range (TBR; d,h) were calculated at the indicated month. $^{\Delta}P < 0.05$, $^{\Delta\Delta}P < 0.01$ versus the baseline in the high residual C-peptide and subgroup aged ≤ 14 years; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ versus the baseline in the low residual C-peptide and subgroup aged > 14 years.

Comparison of HbA1c and glycemic parameters by subgroups in the cohort

Stratified by age

Mean HbA1c decreased from 8.1% to 7.2% in the subgroup aged ≤ 14 years ($n = 69$; $P = 0.014$), but remained stable in the subgroup aged > 14 years ($n = 41$; 7.3% vs 7.6%, $P = 0.7$) at 3 months. No significant changes in TIR was noted over 6 months in both subgroups. However, mean glucose decreased significantly only in the subgroup aged ≤ 14 years (8.1 vs 8.6 mmol/L, $P = 0.015$) at 3 months, and plateaued thereafter. However, TBR increased in the subgroup aged ≤ 14 years (8.7% vs 7.4%, $P = 0.047$) at 3 months, in contrast to no significant change of TBR in the subgroup aged > 14 years.

Stratified by β -cell function

Mean HbA1c in the HRCP subgroup ($n = 40$) was reduced significantly at 3 months (6.9% vs 8.2%, $P = 0.005$) and at 6 months (7.1% vs 8.2%, $P = 0.024$). However, mean glucose decreased in the LRCP subgroup ($n = 70$) at 6 months (7.8 vs 8.4 mmol/L, $P = 0.005$), but not in the HRCP subgroup. Furthermore, TIR also improved from 57.8% to 61.7% at 3 months ($P = 0.023$) and to 62.6% at 6 months ($P = 0.012$) in the LRCP subgroup. No changes in TBR were observed in either subgroup. However, TIR was significantly higher and TBR was much lower in the HRCP subgroup at all time points. Details are shown in Figure 1.

DISCUSSION

This is the first real-life report of FGM initiation in juvenile, adolescent and adult T1DM populations in China. Our study

mainly consisted of two parts: a cross-sectional study and a cohort study. In our analysis, we were able to evaluate clinical factors associated with GV, and more importantly, describe various effects of FGM on overall glycemic control in a real-life setting in our clinic.

In our study population, we demonstrated a significant decrease in overall HbA1c level at 3 and 6 months. More precisely, the mean HbA1c in patients with a baseline HbA1c $> 7.5\%$ significantly improved in contrast with no change in those with a baseline HbA1c $\leq 7.5\%$. Several studies have explored the benefits and safety of using FGM in patients with different HbA1c levels. The results of two RCTs investigating the effect of FGM in reducing hypoglycemia in a recent well-controlled T1DM population (HbA1c $\leq 7.5\%$)²⁷ noted a reduction in TBR^{18,19}. A study by Pickup *et al.*²⁸ indicated that patients with poor glycemic control could gain greater benefits from using CGM. Another RCT conducted in patients with a recent HbA1c $\geq 9\%$ revealed that the application of FGM could improve the frequency of glucose monitoring and the satisfaction of diabetes treatment, although it would not translate into better glycemic control as evaluated by decreased HbA1c after 6 months of FGM usage²⁹. It follows then that the benefits of applying FGM in different populations are not exactly the same. However, in our study population, the improvement of HbA1c was accompanied by an increase in TBR at 3 months in patients under 14 years. Parents play a significant role in the management and monitoring of their children with T1DM. Studies have previously revealed that many parents of young children with T1DM exhibit symptoms of anxiety, depression, stress, and distress^{23,30}. Actually, we had investigated the anxiety

and distress of parents of our patients under 14 years as soon as we noticed the phenomenon that children with T1DM in our clinic tend to develop more hypoglycemia, more often due to excessive parental intervention or psychological stress under clinical circumstances by questionnaires: State-Trait Anxiety Inventory (STAI-6)³¹ and Parent-Diabetes Distress Scale³², and we found that the mean STAI-6 score was 47.8, suggesting that anxiety was common in parents; while the mean P-DDS item score was 1.7, which should be considered as little or no depression (data not shown). In this regard, we speculated an increase of TBR in children might probably partly explained by (1) excessive inappropriate intervention due to patients' anxiety; (2) unfamiliar with the Freestyle Libre[®] device in the first 3 months, and lacked experience in handling proliferating real-time feedback of immediate abnormal blood glucose. Moreover, by educating parents in time soon after an increase in hypoglycemia was observed 3 months post-initiation of FGM, TBR had already alleviated at the 6-month follow-up. Since we did not take parental psychological effects on children glycemic control into consideration in advance, which may be a limitation of our study.

With respect to beta-cell function evaluation, FCP and 2hCP are frequently used in clinical practice due to their good consistency with MMTT or glucagon stimulated C-P^{33–36} and the ability to predict beta-cell function in autoimmune T1DM^{37,38}. In the landmark Diabetes Control and Complications Trial (DCCT) study, the role of beta-cell function was first demonstrated in T1DM patients using intensive insulin therapy³⁹. The results showed that patients with C-P levels between 200 and 500 pmol/L after MMTT had significantly lower HbA1c levels, daily insulin dosage, and the incidence of severe hypoglycemia than those with C-P <200 pmol/L. Sherr *et al.*⁴⁰ showed that TBR in youth with newly-onset T1DM who retain high residual beta-cell function (peak C-P ranging from 460 to 1960 pmol/L) was not different from that in non-diabetic patients, and CV was significantly lower than that in patients with islet failure. Moreover, Gibb *et al.*⁴¹ found that the preserved C-P secretion group (10–200 pmol/L) had significantly lower CV, TBR and hypoglycemia events than those in the failure group (<10 pmol/L). However, no significant difference in TIR was noted. In our cross-sectional analysis, the HRCF group had a significantly shorter duration of diabetes, higher TIR, and lower mean glucose and GV. Accordingly, FCP was positively correlated with TIR and negatively correlated with GV parameters. We revealed an association between HRCF and clinically higher TIR.

Mean HbA1c and mean glucose levels in the LRCP subgroup were reduced significantly at 3 and 6 months. Additionally, TIR was also found to increase. However, regardless of the remarkably improvements in TIR and mean glucose levels, TIR was still significantly higher and TBR was much lower in patients with HRCF at all time points. The DCCT established that a stimulated C-P concentration ≥ 200 pmol/L at study entry among subjects with up to a 5-year diabetes duration is

associated with favorable metabolic and clinical outcomes (lower HbA1c, blood glucose and daily insulin dosage) over the subsequent 7 years of follow-up³⁶. Moreover, a study reported that TIR of patients with a stimulated C-P >200 pmol/L after MMTT increased after exercise, while it decreased in those with peak C-P ≤ 200 pmol/L⁴². Thus it can be inferred that T1DM patients with LRCP in our study population may gain greater benefits from using FGM. Nevertheless, these pronounced benefit brought by FGM in glycemic control was still inferior to the HRCF itself, which has not previously been reported.

Children and adolescents with T1DM should make a greater effort to maintain euglycemia due to their growth needs⁴³. During the transition from childhood to adolescence, substantial physical and psychological changes make it difficult for this population to achieve optimal glycemic control⁴⁴. The benefits of CGM in children and adolescents with T1DM have been gradually highlighted as it is more widely available^{21,22,45}, while in the landmark Juvenile Diabetes Research Foundation (JDRF) study reported no significant improvement in HbA1c after commencement of CGM in the 8–14 years group⁴⁶, implying that the role of CGM in adolescents is not entirely clear. As mentioned before, our clinic has a large proportion of children with T1DM, in whom DKA at diagnosis was common. However, DKA at diagnosis of T1DM predicts persistently elevated HbA1c levels and poor long-term glycemic control independent of demographic and socioeconomic factors⁴⁷, and decline in C-P levels was associated with the age at T1DM onset²⁴. Our subjects were divided into a ≤ 14 years subgroup and >14 years subgroup. Since in China, children are usually defined as age under 14 years old. Based on our national conditions, 14 years of age is the watershed between junior school and senior high school, and the self-care ability has always thought to be apparently improved when attending senior high school. Children under 14 years of age, on the other hand, are still be taken care of by their parents most of the time. Surprisingly, we found a decrease in HbA1c at 3 months in the ≤ 14 years subgroup in contrast with no statistical change in HbA1c in the >14 years subgroup. What's more, mean glucose was also reduced significantly in the ≤ 14 years subgroup. However, TBR also increased at 3 months in this subgroup. Regarding this outcome, we speculated that age-appropriate diabetes education and parenting efficacy play a role in glycemic control in children.

Our experiment had certain advantages: to our knowledge, this is the first longitudinal study describing the changes in glycemic control after FGM initiation across a wide age group in China. Due to our large proportion of young T1DM patients, we were able to identify different efficacies of initiating FGM in different subgroups based on age and beta-cell function, and based on the results we found, we raised the question of whether age-appropriate diabetes education is needed. Moreover, the parenting effect on glycemic control and the psychological condition of parents should be given more attention in clinical practice. We acknowledge that there are several limitations. First, the 6-month follow-up period was not long enough

to provide a long-term effect of FGM on overall glycemic control. Second, potential biases caused by uncertain confounding factors were difficult to rule out in such real-world studies. Other limitations were the relatively small sample size and the single-centre nature of the study.

In conclusion, our results indicated that HRCF was associated with less GV. Moreover, 6-month application of FGM showed a reduction in HbA1c, especially in patients with poor glycemic control, pediatric patients and those with HRCF. However, an increase in hypoglycemia was also observed in patients under 14 years at 3 months. Pertaining to the subgroup analysis, we raised questions regarding age-appropriate diabetes care and attention to parents' psychological stress for T1DM children. In addition, further research is needed to explore whether early contact with FGM devices leads to better self-management of T1DM and quality of life.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The study protocol was approved by the Ethics Review Committee of the Second Xiangya Hospital of Central South University (approval number: 2019-198; date granted: 12 November 2019), and it was carried out in accordance with the Declaration of Helsinki.

Informed consent: Signed informed consent was obtained from each participant.

Approval date of registry and the registration no. of the study/trial: N/A.

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