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ORIGINAL RESEARCH

Intermittent Use of Flash Glucose Monitoring Improves Glycemic Control in Chinese Older Patients with Type 2 Diabetes Mellitus

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Objective: To explore the efficacy and safety of intermittent use of flash glucose monitoring (FGM) for improving glycemic control in Chinese elderly patients with type 2 diabetes mellitus (T2DM).

Methods: This is a prospective observational study involving patients with T2DM aged ≥60 years. The study period spans 12 weeks, with participants wearing FGM at weeks 0, 5, and 10. Participants were divided into two subgroups based on HbA1c at enrollment: < 7.0% and ≥7.0%. The primary outcome of the study was HbA1c level. Secondary outcomes included time in range (3.9–10mmol/L) (TIR), time below range (<3.9mmol/L) (TBR), time above range (>10.0mmol/L) (TAR), and glycemic variability (GV).

Results: A total of 68 patients completed the 12-week FGM follow-up (age 67.9 ± 5.2 years; BMI 25.4 ± 3.3kg/m²). Overall findings revealed that compared to baseline, HbA1c decreased from 7.81 ± 1.25% to 7.44±1.10% after 12 weeks of intermittent wearing of FGM (p <0.001). In the subgroup analysis with HbA1c ≥7.0%, the results showed a significant reduction in HbA1c of 0.51mmol/L after 12 weeks (8.36 ± 0.95% vs 7.75 ± 0.97%, p < 0.001). And there was a significant reduction in TBR in the subgroup with HbA1c < 7% (p = 0.028). Multiple linear regression analysis showed that the baseline HbA1c (β = −0.529, P<0.001), duration of T2DM (β = 0.341, P = 0.001), and the frequency of sensor use (β = −0.269, P = 0.043) were associated with the reduction in HbA1c level.

Conclusion: Intermittent use of FGM is associated with an improvement in glycemic outcomes and reduces the risk of hypoglycemia in Chinese elderly patients with T2DM.

Keywords: flash glucose monitoring, type 2 diabetes mellitus, HbA1c, time in range

Introduction

Research indicates that approximately 537 million adults worldwide were living with diabetes mellitus (DM) in 2022, a figure projected to reach 783 million by 2045.[1] Type 2 diabetes mellitus (T2DM), the predominant form of DM, accounts for an estimated 90% to 95% of all diagnosed cases of DM.[2] With the increasing aging of the population and the gradual urbanization of lifestyles, the epidemiological population of T2DM is dramatically shifting towards the elderly (especially those aged 60 to 79 years).[3] The prevalence of T2DM has increased markedly in the aging population over the past 50 years, with approximately half of current T2DM patients being older than 65 years and this trend is expected to continue in the coming decades.[4]

Elderly patients with T2DM are at an increased risk of hypoglycemia due to their long medical history, presence of multiple comorbidities, and polypharmacy,[5] as well as subtle symptoms that are prone to being overlooked.[6] This condition is strongly associated with adverse outcomes, including falls, cardiovascular and cerebrovascular diseases, and increased all-cause mortality.[7] Given the heterogeneity of older adults with T2DM, it is essential to adopt an individualized approach to avoid over-treatment and hypoglycemia in frail older adults and the undertreatment of otherwise healthy individuals.[8]

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Glucose monitoring helps to identify hypoglycemia early, assess the degree of glucose metabolism disorders, and develop a personalized glycemic management plan.[9] Traditional glucose monitoring methods, such as HbA1c, glycated albumin, and self-monitoring of blood glucose (SMBG), do not provide real-time glucose data or warn of asymptomatic glucose abnormalities.[10] Flash glucose monitoring (FGM), also known as ambulatory glucose monitoring, is uniquely suited for identifying insidious hyperglycemia or hypoglycemia by providing an ambulatory glucose profile (AGP) to understand the patient's glucose fluctuations.[11]

Several studies have shown that continuous use of FGM for 12 weeks or longer is beneficial for patients with T2DM, including significantly reducing HbA1c levels, lowering the rates of acute diabetes complications or hospitalization, reducing the risk of hypoglycemia, and improving treatment satisfaction.[12–14] A recent study indicated that initiation of FGM was associated with a clinically and statistically significant improvement in HbA1c in a real-world setting at 3–6 months.[15] Another multicenter randomized trial showed that compared with SMBG, continuous wearing of FGM for three months in T2DM individuals with marginally increases TIR and significantly reduces hypoglycemic exposure.[16] However, long-term use of FGM is expensive and difficult for patients to adhere to. Therefore, this study intends to explore whether intermittent use of FGM could improve glycemic control in Chinese elderly patients with T2DM.

Methods

Study Design and Participants

This prospective observational study was registered at ClinicalTrials.gov with the registration number NCT03785301. This research was approved by the ethics committee of Nanjing First Hospital and was conducted in accordance with the principles of the 1964 Declaration of Helsinki, as revised in 2013. During the implementation of the study, we modified the enrollment protocol, adapting from a randomized controlled study design to a self-controlled before-and-after design due to a lack of study budget. The new study protocol did not increase the risk to subjects. Furthermore, written informed consent was obtained from each patient. Participants were identified through the endocrinology outpatient department at Nanjing First Hospital. Individuals were invited to participate via phone or on-site, and interested patients were referred to the research centers conducting the study procedures. Screening occurred following the initial physician–patient consultation unless it was already clear that the patient would not fulfill the inclusion criteria of the study.

Data Collection Process

The baseline demographic data of the patients was obtained through patient interviews or from medical records. This data included age, sex, body mass index (BMI), duration of T2DM, presence of comorbidities (including cardiovascular diseases, cerebrovascular disease, and peripheral atherosclerosis); types and dosages of oral antidiabetic drugs (OADs), and insulin. Blood samples were collected, and relevant laboratory parameters, including baseline and endpoint HbA1c levels, were measured at local facilities.

The inclusion criteria were as follows: age of 60 years or older, T2DM duration of six months or longer, BMI ranging from 18 to 35 kg/m², and the patient's weight and medication regimen must have been stable for the three months preceding the screening.

The following criteria led to exclusion: diagnosis of type 1 diabetes mellitus (T1DM), acute illnesses or infections, use of glucagon-like peptide 1 receptor agonists (GLP-1RAs), severe liver and renal dysfunction, use of glucocorticoids within three months prior to the study period, history of cancer treatment, and subjects who, or their caregivers, were unable to comply with FGM instructions.

Before initiating this study, the sample size was determined as follows. Assuming a moderate effect on HbA1c after three months of intervention, a Cohen's effect size of 0.5, a significance level of 0.05, and power of 0.95. Utilizing G*Power software for sample size calculation, it was found that 54 patients would be needed to disprove the null hypothesis (no difference between baseline and after three months of intervention in a two-sided paired *t*-test). We ultimately enrolled 68 patients in the study to ensure adequate statistical power. Eligible subjects had a FGM sensor inserted in the posterior upper arm (FreeStyle Libre Flash CGM System, Abbott Diabetes Care) after the initial follow-up visit. They were advised to receive FGM as frequently as possible throughout the day to prevent scanning intervals from

exceeding eight hours. The entire study period spanned 12 weeks, with all participants wearing the FGM for 14 days at Weeks 0, 5, and 10. At the end of each monitoring session, patients were instructed to return to the center, where FGM data were downloaded, and AGPs were generated for review by the primary provider. Regardless of whether patients were wearing FGM, we asked them to continue SMBG with the same frequency as their previous lifestyle. Doctors adjusted hypoglycemia treatment, and diabetes specialist nurses provided monthly education about self-management of diet and exercise based on FGM data. The first two weeks were considered the baseline period, weeks 5 to 7 constituted the follow-up period, and the last two weeks marked the study endpoint.

The research team and healthcare professionals were instructed not to modify the treatment regimen except for safety reasons, in which case participants were excluded from data analysis.

Outcomes Measures

Participants were divided into two subgroups based on their HbA1c levels at enrollment: < 7.0% and ≥ 7.0%. The primary outcome of this prospective study was the HbA1c level. Secondary outcomes included mean glucose (MG), time in range (3.9–10.0mmol/L) (TIR), time above range >10.0mmol/L (TAR), time below range <3.9 mmol/L (TBR), glucose variability (GV) (calculated as the coefficient of variation, %CV = SD / MG×100%), and compliance with FGM use (percentage of sensor data captured). TIR, TBR, and TAR are expressed as percentages of the day.

Statistical Analysis

Categorical variable data are presented as numbers and percentages. We report variables as medians (ranges) for non-normally distributed data and as mean±SD for normally distributed data. To compare each parameter between baseline and study endpoints, paired t-tests for unskewed variables and Wilcoxon signed-rank tests for skewed variables were performed. Multiple linear regressions were performed to identify associations between factors, such as age, sex, T2DM duration, baseline HbA1c level, and frequency of sensor use with changes in HbA1c levels. Missing data from the sensor-based FGM system glucose levels were excluded when estimating each parameter. All statistical analyses were conducted using IBM SPSS version 26.0 for Windows. A p-value < 0.05 was considered statistically significant.

Results

A total of 80 patients were screened between March 2019 and October 2019 in the study. Of these, 12 patients dropped out before completing the study due to withdrawal of consent (n = 5), the sensor falling off the arm (n = 4), and missing data (n = 3). The remaining 68 patients underwent analysis of their glycemic control (Figure 1). The baseline clinical characteristics for the HbA1c < 7.0% group (N = 14) and ≥7.0% group (N = 54) are detailed in Table 1. Overall, the mean baseline HbA1c was 7.8±1.2%, with a mean duration of 11.6±7.4 years and a mean BMI of 25.4±3.3kg/m². There was a higher proportion of participants using premixed insulin + OADs in the subgroup with HbA1c≥7.0%.

Older T2DM adults at baseline exhibited a median TIR of 68.2% (IQR = 53.47–81.1), a median TBR of 1.6% (IQR = 0.3–4.4), a median TAR of 27.7% (IQR = 13.2–43.9). In the sixth week, the median TIR was 67.5% (IQR = 50.6–81.3), TBR was 0.9% (IQR = 0.1–4.6), and TAR was 25.7% (IQR = 10.32–49.2). After 12 weeks of follow-up, the median TIR increased to 72.1% (IQR = 61.9–83.5), TBR was 0.8% (IQR = 0–2.9), and TAR was 21.8% (IQR = 9.0–37.0) (Figure 2).

Table 2 presents the mean and SD for HbA1c changes during the study period. In the overall analysis, the primary outcome of HbA1c decreased from a baseline of 7.81±1.25% to 7.44±1.10% at the end of the follow-up period (p <0.001). In the subgroup analysis of HbA1c ≥7.0%, the mean (±SD) HbA1c was significantly decreased by an average of 0.51mmol/L after the 12-week visit (8.36±0.95% vs 7.75±0.97%, p <0.001), whereas, there were no significant differences in the subgroup analysis with HbA1c <7%. Table 3 displays the results of the multiple linear regression, in which the change of HbA1c was the outcome. Both baseline HbA1c level (β=−0.529, p<0.001), duration of T2DM (β=0.341, p=0.001), and frequency of sensor use (β=−0.269, p=0.043) predicted improvement of HbA1c. The higher the baseline HbA1c levels and the shorter the T2DM duration of the participants, the more significant the improvement in HbA1c after using FGM. Similarly, the more frequent the daily sensor use, the more noticeable the reduction in HbA1c following the use of FGM.

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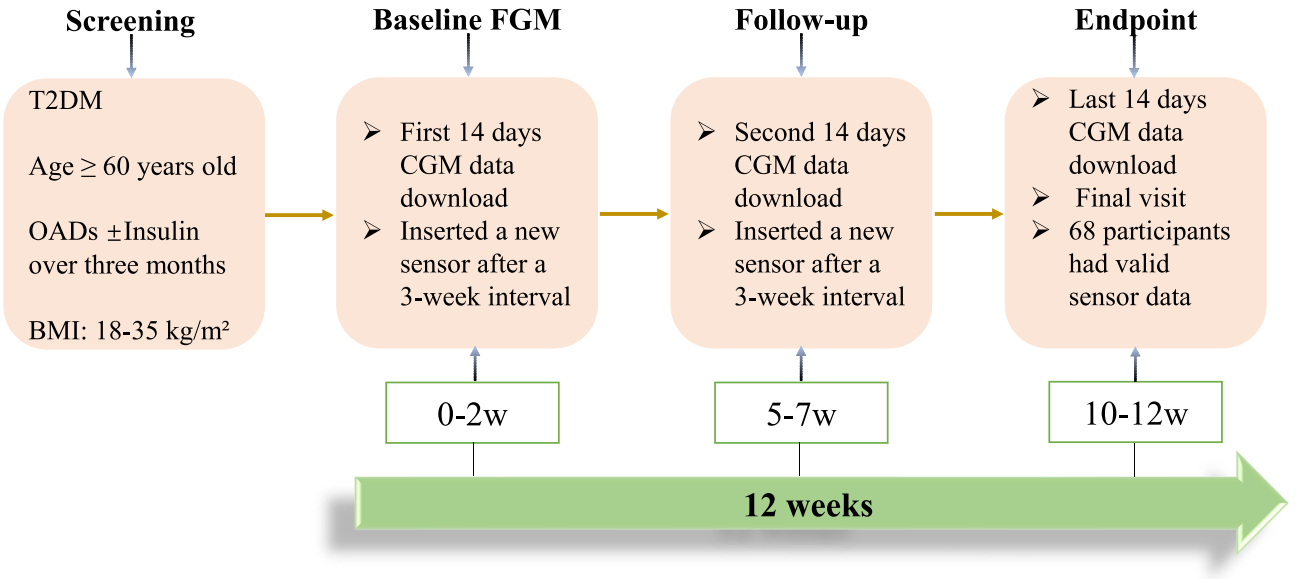

Figure 1 The study protocol.
Abbreviations: T2DM, type 2 diabetes mellitus; OADs, Oral Antidiabetic Drugs; BMI, Body Mass Index; FGM, flash glucose monitoring; CGM, continuous glucose monitoring.

Table 4 showed a greater improvement of TIR in individuals with a HbA1c ≥7.0% (59.7±23.6% vs 66.9±19.3%, p = 0.002), whereas in the HbA1c <7% group, changes in TIR showed no significant difference. In the HbA1c <7.0% participants, there was a significant decrease in TBR [8.9 (0.5, 12.6) vs 2.7 (0.3, 10.5), P = 0.028]. And in the HbA1c ≥7.0% subgroup, there was a significant decrease in MG (9.3 ± 2.0mmol/L vs 8.8 ± 1.7 mmol/L, P = 0.006), a significant decrease in TAR (38.2 ± 24.6% vs 30.7 ± 20.7%, P = 0.003). Moreover, within the HbA1c ≥ 7.0% group, glucose fluctuation also significantly improved (GV: 31.3 ± 7.1% vs 29.7 ± 5.7%, P = 0.047). The mean FGM glucose concentrations across the 24 hours of the day are shown in Figure 3 and highlight the marked improvement from baseline to 12 weeks during both daytime and nighttime hours in those with baseline HbA1c ≥7.0% using FGM.

No side effects related to the use of FGM were reported. There was no episode of severe hypoglycemia occurred throughout the follow-up period.

Discussion

This real-world prospective clinical study observed significant improvement in HbA1c levels among Chinese elderly patients with T2DM after three months of intermittent use of FGM. Generally, we observed a significant reduction in

Table 1 Clinical Baseline Characteristics Overall and by HbA1c

Characteristic	Overall	HbA1c< 7%	HbA1c≥7%
N	68	14	54
Sex, male (n, %)	46, 67.6	8, 57.1	24, 44.4
Age (years)	67.9±5.2	66.4±5.0	68.3±5.2
HbA1c (%)	7.8±1.2	6.1±0.6	8.3±0.9
Diabetes duration (years)	11.6±7.4	10.6±6.7	12.5±80
BMI (kg/m^2)	25.4±3.3	25.2±2.4	25.4±3.5
Premixed insulin (n, %)	12, 17.6	4, 28.6	8, 14.8
Oral Antidiabetic Drugs (OADs; n, %)	16, 23.5	4, 28.6	12, 22.2
Premixed insulin + OADs (n, %)	39, 57.4	5, 35.7	34, 63.0
Drug-free (n, %)	1, 1.5	1, 7.1	0, 0

Abbreviations: N, number; BMI, Body Mass Index.

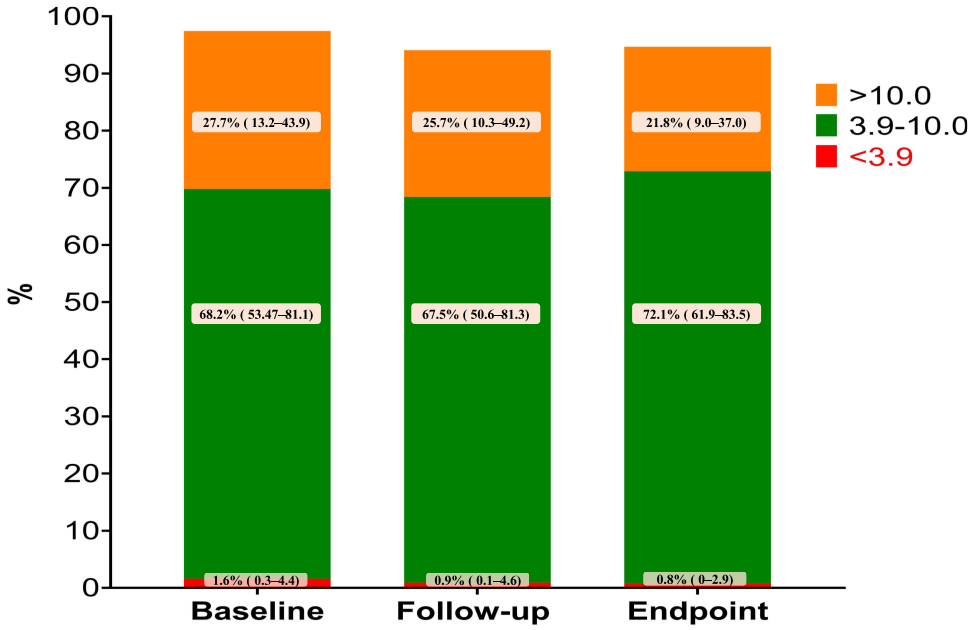

Figure 2 Glucose profile at baseline and after 12 weeks of intermittent sensor use.

HbA1c from baseline of 7.81±1.25% to 7.44±1.10% at the end of the 12-week follow-up period ($p < 0.001$). Notably, a significant reduction in TBR and GV was observed in the subgroup with HbA1c < 7%. Moreover, in the subgroup analysis with HbA1c ≥7.0%, patients experienced a significant reduction in HbA1c of 0.51mmol/L after 12 weeks (8.36 ± 0.95% vs 7.75 ± 0.97%, $p < 0.001$).

The large treatment effect observed for the HbA1c ≥7.0% group is clinically relevant, considering that this HbA1c group is at a higher risk of micro- and macrovascular complications related to poor glycemic control.[17–19] Limited data

Table 2 The Changes in HbA1c During the Study Period Overall and by HbA1c

	0W HbA1c (%)	12W HbA1c (%)	ΔHbA1c (%)	*P* value
Total	7.81±1.25	7.44±1.10	−0.37	<0.001
HbA1c < 7%	6.10±0.62	6.24±0.63	+0.14	0.516
HbA1c ≥ 7%	8.36±0.95	7.75±0.97	−0.51	<0.001

Notes: Significance at a P value of <0.05. ΔHbA1c: changes in HbA1c.

Table 3 Multiple Linear Regression Analyses of ΔHbA1c (Dependent Variable)

	SE	Standard β	P value
Age	0.015	0.108	0.281
Gender	0.161	−0.193	0.082
Baseline HbA1c	0.060	−0.529	<0.001
T2DM duration	0.010	0.341	0.001
BMI	0.021	0.109	0.281
Frequency of sensor use	0.032	−0.269	0.043

Notes: Significance at a P value of <0.05. ΔHbA1c: changes in HbA1c. ΔHbA1c was regarded as the dependent variable, and independent variables included age, gender, baseline HbA1c, T2DM duration, BMI, and frequency of sensor use. β: regression coefficient.
Abbreviation: BMI, Body Mass Index.

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Table 4 Glycemic Outcomes Among Participants by HbA1c Arm

Variable	HbA1c < 7%			HbA1c ≥ 7%		
	FGM1	FGM3	P* value	FGM1	FGM3	P* value
MG (mmol/L)	6.8±1.0	6.9±1.1	0.586	9.3 ± 2.0	8.8 ± 1.7	0.006
GV (%)	32.6±10.5	30.8±9.4	0.025	31.3±7.1	29.7±5.7	0.047
TIR (%)	80.2±14.4	82.5±16.1	0.063	59.7±23.6	66.9±19.3	0.002
TAR (%)	11.0±10.0	11.6±12.9	0.723	38.2±24.6	30.7±20.7	0.003
TBR (%)	8.9 (0.5, 12.6)	2.7 (0.3, 10.5)	0.028	1.0 (0.3, 2.8)	0.7 (0.0, 2.6)	0.671

Notes: Significance at a P value of <0.05. *: paired *t*-test between FGM 1 and FGM 3. FGM 1: the first time FGM; FGM 3: the last time FGM.

Abbreviations: MG, mean glucose; GV, glucose variability; TIR, time in range; TAR, time above range; TBR, time below range.

from clinical trials and observational studies suggest that FGM may induce a larger treatment effect among patients with higher HbA1c or lower TIR at baseline, although most studies have included patients on intensive insulin therapy.[20] A post hoc analysis of the DIAMOND trial evaluating continuous glucose monitoring (CGM) use in adults with both T1DM and T2DM on intensive insulin therapy reported the greatest HbA1c improvement in those with an initial HbA1c value ≥ 9%.[21] A recent meta-analysis also showed that FGM led to modest but statistically significant declines in HbA1c among individuals with T2DM.[22] Our results are consistent with and expand these findings to older T2DM patients. The marked reduction in time spent with glucose > 10.0mmol/L and < 3.9mmol/L in the subgroup with baseline HbA1c values ≥ 7.0% was achieved without changing the medication regimen. However, in the HbA1c <7% group, changes in HbA1c showed no significant difference. This may be attributed to the fact that for patients with higher baseline HbA1c levels, the FGM high-glucose alerts could prompt patients to take corresponding actions, such as reducing food intake or increasing physical activity, thereby achieving the effect of improving glycemic control.[23] Nevertheless, a previous study[24] found that FGM use in T2DM with intensive insulin therapy results in no difference in HbA1c change, which may be due to differences in enrollment populations.

These findings provide evidence for the potential benefits of intermittent wearing of FGM in a broader population of T2DM patients. The higher the baseline HbA1c level, the shorter the duration of T2DM, and the more frequent the scans, the greater the benefit to the patients. Therefore, the use of FGM for a short period as soon as possible following diagnosis would provide T2DM patients with daily biofeedback on their glycaemic control that could help to foster the

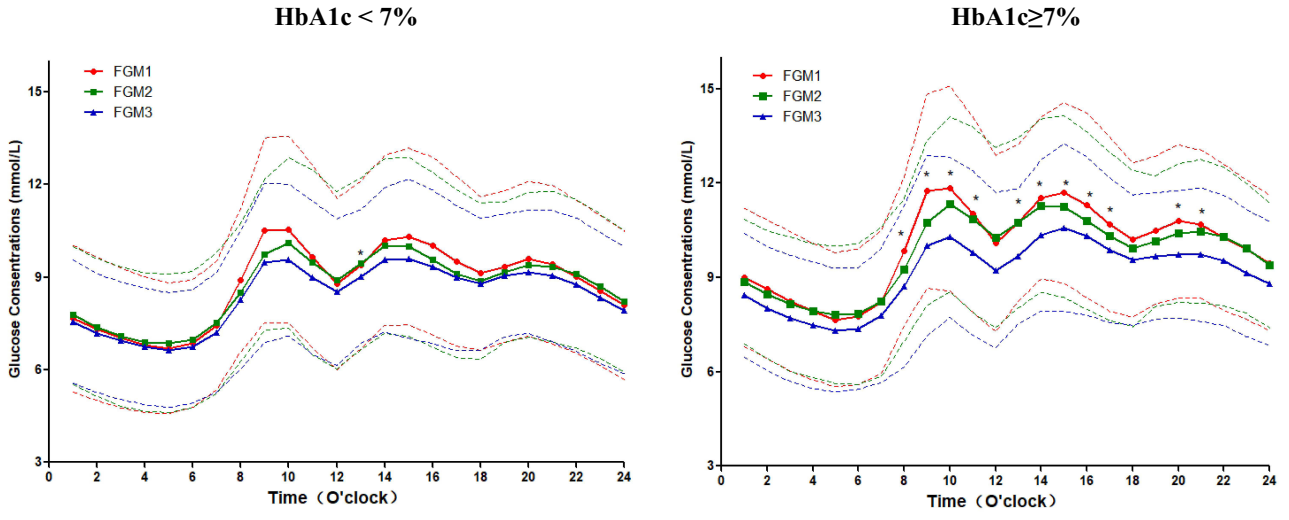

Figure 3 Mean glucose over 24 h by baseline HbA1c.

Notes: The solid line represents the mean glucose and the dashed line represents the SD. * represents a statistically significant difference between FGM3 compared to FGM1. FGM 1: the first time FGM; FGM 2: the second time FGM; FGM 3: the last time FGM.

healthy behavioral changes.[11] Additionally, a previous study indicated that the frequency of viewing instantaneous FGM information by patients is related to better glycemic control, which is consistent with our results.[25] Carlson et al[26] suggested that the improvements in HbA1c after initiating FGM might be influenced by various factors, including basal insulin dose titration supported by FGM data, adjustments to oral medications, and changes in lifestyle or behavior, all of which could contribute to lowering HbA1c. Another study indicated that without changing the therapy regimen, T2DM patients have improved glycemic control by wearing FGM, achieving these benefits solely through real-time blood glucose guidance for lifestyle improvements such as diet structure and exercise timing.[27]

FGM also provides new indicators of glycemic control related to diabetes complications. TIR is closely related to the risk of diabetic microvascular complications. In the present study, we observed significant improvements in TIR from a baseline of 59.7±23.6% to 66.9±19.3% in the HbA1c ≥ 7.0% group ($p = 0.002$). This outcome is consistent with a decrease in HbA1c, as previous studies have shown a robust correlation between TIR and HbA1c.[28]

Importantly, this improvement in glycemic control observed in this study was not accompanied by increased rates of hypoglycemia. The present research showed that TBR and GV were significantly reduced after intermittent wearing of FGM for 12 weeks in the HbA1c < 7% group. In contrast, there was no significant change in TBR in the subgroup with HbA1c ≥7%. This discrepancy may be due to the fact that patients with HbA1c < 7% tend to have lower nocturnal blood glucose (as shown in Figure 3). The FGM low-glucose alerts could prompt patients to take measures to alleviate hypoglycemia, leading to a more pronounced improvement in TBR for this group. A similar study in Belgium assessed the effectiveness of FGM in 1913 adults with T1DM.[29] Investigators reported significant reductions in hospital admissions for severe hypoglycemia and diabetic ketoacidosis (from 3.2% to 2.2%; $p = 0.031$), the number of patients reporting severe hypoglycemic events (from 14.6% to 7.8%; $p < 0.0001$), and rates of hypoglycemic comas (from 2.7% to 1.1%; $p = 0.001$) following one year of FGM use. Another study indicated that the availability of glucose data provided by the FGM system was associated with a reduction in resultant hospitalizations in individuals with T2DM, whether due to hypoglycemia or hyperglycemia.[30] Using FGM can help to identify patterns of GV, allowing individuals with T2DM and health-care professionals to take action to reduce them.[31]

This study presents several limitations that require caution in interpreting the results. Firstly, the primary limitation is the single-arm design, which lacks the proof strength of a randomized controlled study design. This limitation precludes the calculation of the potential "placebo effect" on observed improvements and prevents the establishment of causality between the intervention and observed benefits. The absence of a control group also complicates the exclusion of selection bias, measurement bias, and confounding factors, hindering our ability to attribute the findings to real-world clinical efficacy. Secondly, our study duration was relatively short. Future research should encompass longer and larger randomized controlled trials (RCTs) to compare the intermittent use of FGM with traditional SMBG on glycemic control, thereby validating our findings. However, there is limited convincing data with a paucity of long-term research in this area, so this real-world study is nonetheless expected to represent a meaningful contribution. Lastly, FGM sensor placement was performed at the center, therefore, we did not assess the elderly's ability to manage it by themselves. Despite these limitations, our results are unique and innovative with respect to Chinese older T2DM patients, and we estimated the HbA1c and TIR using a sensor-based FGM system and confirmed the results from trials.

Conclusion

The intermittent use of FGM improves glycemic control and reduces the risk of hypoglycemia in Chinese elderly T2DM patients, particularly in those with a shorter duration of T2DM, poorer glycemic control, and a higher frequency of sensor use. Larger and long-term RCTs are necessary to validate our findings.

Data Sharing Statement

The datasets generated for this study are available on request to the corresponding author.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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